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# Baseline Values and Sotalol-Induced Changes of Ventricular Repolarization Duration, Heterogeneity, and Instability in Patients With a History of Drug-Induced Torsades de Pointes

Jean-Philippe Couderc, PhD, MBA, Stefan Kaab, MD, PhD, Martin Hinterseer, MD, Scott McNitt, MS, Xiaojuan Xia, MS, Anthony Fossa, PhD, Britt M. Beckmann, MD, Slava Polonsky, MS, and Wojciech Zareba, MD, PhD, FACC

The authors investigated whether computerized parameters quantifying ventricular repolarization delay, heterogeneity, and instability characterize individuals who developed drug-induced Torsades de Pointes. Assessing an individual's propensity to Torsades de Pointes when exposed to a QT-prolonging drug is challenging because baseline QT prolongation has limited predictive value. Five-minute digital 12-lead electrocardiograms were acquired at baseline and after a sotalol challenge in 16 patients who had a history of Torsades de Pointes in the context of a QT-prolonging drug and 17 patients who did not have such history. Computerized measurements of QTc, T peak to T end intervals (TpTe), TpTe/QTc, and QT variability were implemented, and novel quantifiers of ventricular repolarization heterogeneity from the early (ERD) and late (LRD) part of the T wave were investigated. Compared with electrocardiograms of patients without a history of Torsades de Pointes, the baseline electrocardiograms of

patients with a history of Torsades de Pointes had a longer QTc and an increased repolarization heterogeneity of the early part of the T wave (ERD<sub>30%</sub>:  $44 \pm 13$  vs  $35 \pm 8$  ms,  $P = .02$ ). On sotalol, the electrocardiograms from individuals with Torsades de Pointes revealed a delay of the terminal part of the T wave that was not present in patients without Torsades de Pointes (TpTe:  $27 \pm 40$  vs  $-2 \pm 21$  ms,  $P = .02$ ; LRD<sub>70%</sub>:  $20 \pm 29$  vs  $2 \pm 4$  ms,  $P = .04$ ). Results suggest that the electrocardiogram abnormalities characterizing patients with a history of Torsades de Pointes are (1) an increased repolarization heterogeneity at baseline and (2) a sotalol-induced prolongation of the terminal part of the T wave.

**Keywords:** QT interval; Torsades de Pointes; electrocardiogram; sotalol

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**D**rug-induced Torsades de Pointes (TdP) have been associated with an increasing number of cardiac and noncardiac marketed drugs commonly affecting the rapid components of the delayed rectifier potassium current ( $I_{kr}$ ) of the myocardial cells. However, if  $I_{kr}$  inhibition and QT interval prolongation are associated with the occurrence of drug-induced TdP, they should not constitute a reason for considering a drug to be proarrhythmic.<sup>1</sup> The dissociation between drug-induced QT interval prolongation<sup>2</sup> and an increased risk of arrhythmias is supported by the

existence of drugs associated with a QT interval prolongation but a limited history of TdP such as tamoxifen,<sup>3</sup> carvedilol,<sup>4</sup> and, more recently, ranolazine, which seems to prolong the QT interval duration while reducing ventricular heterogeneity.<sup>5</sup> Consequently, the rejection of a novel drug because of its QT-prolonging effect is a rather dubious strategy because it might deprive patients of a valuable medication. Improving the assessment of drug cardiotoxicity linked to the ventricular repolarization process could depend on the development of better electrocardiographic markers than QT prolongation.

The triggering mechanism(s) of drug-induced TdP remains to be elucidated, but there are several interesting alternatives currently proposed: Hondeghem et al suggested the TRiAD concept, emphasizing the role of action potential triangulation, reverse use dependence of the drug, and repolarization instability.<sup>6,7</sup> The triangulation of the action potential and the heterogeneity of electrical properties of the cells across the myocardium are consistent with the proarrhythmic factors described by Belardinelli et al<sup>8</sup>: the transmural dispersion of repolarization and the promoting role of early after-depolarization.<sup>9,10</sup> Finally, the concept of repolarization reserve described by Roden<sup>11</sup> emphasizes the role of the interplay of ion currents involved in cardiac repolarization. These currents provide functional redundancy, or “reserve,” and can protect an individual against excessive QT prolongation by drugs. Also, gender, hypokalemia, predisposing DNA polymorphism, and environmental factors are recognized to be potential modulators of the ventricular repolarization process. They can lead to a reduced repolarization reserve and an increased propensity to arrhythmias.

In this study, we hypothesize that patients with a history of drug-induced TdP have a certain level of repolarization impairment (heterogeneity, reduced repolarization reserve, and instability) that can be measured from their digital surface electrocardiogram (ECG). Increased QT duration, repolarization heterogeneity, and QT variability are investigated at baseline and when the patients are exposed to a torsadogenic drug such as sotalol.

## METHOD

### Study Population

The patients were enrolled after being admitted to the University Hospital of Munich, Germany, for

documented TdP in the context of a drug with QT-prolonging potential: sotalol, sumatriptan, amiodarone, bisacodyl, cipramil, furosemide, clarithromycin, erythromycin, or roxythromycin. The patients were enrolled for an evaluation of the individual level of repolarization reserve, and all patients signed informed consent to receive doses of sotalol as described previously.<sup>12</sup> They were all genetically tested for the presence of a mutation of the major LQTS genes using standard genotyping techniques (genomic DNA was prepared from lymphocytes, and amplification of KCNQ1, KCNH2, KCNE1, KCNE2, and SCN5A using polymerase chain reactions was performed, followed by direct sequencing of these major LQT-disease genes). The control group consisted of patients who were started on sotalol for the prevention of paroxysmal atrial fibrillation and had given informed consent to enter the study.

### Study Protocol and Electrocardiogram Recordings

The study protocol was described by Kaab et al.<sup>12</sup> Briefly, dl-sotalol was given intravenously at a constant rate over a 20-minute interval at a dose of 2 mg/kg body weight in 50 mL of a 0.9% saline solution in a group of individuals with (+TdP) and without (-TdP) a history of drug-induced TdP. Tests were performed in the morning. Sotalol was injected to unmask latent repolarization abnormalities while patients were closely and continuously monitored in the intensive care unit. Continuous 5-minute surface 12-lead ECG recordings (Mortara Instrument, Milwaukee, Wisconsin) were acquired at rest in the supine position at baseline and at 20-minute steady-state phase after injection. We obtained access to 2 ECG tracings per individual at baseline and on peak concentration of the drug.

The measurements of the PR and QRS durations from the 5-minute ECGs were provided by the Mortara SuperECG software (SuperECG, Mortara Instrument). The RR intervals and repolarization intervals were based on technology developed at the University of Rochester Medical Center (Rochester, New York). The COMPAS software provided the location of the end of the T wave based on a technique identifying the crossing point between the baseline and the descending slope of the T wave (least squares technique).<sup>13</sup> The apex of the T wave relied on a method using a parabola fit of the T wave where the maximum of the parabola identified the location of the apex. Baseline wandering was adjusted using Spline interpolation.<sup>13</sup> The amplitude of the T wave was measured at the apex of the T wave.<sup>14</sup>

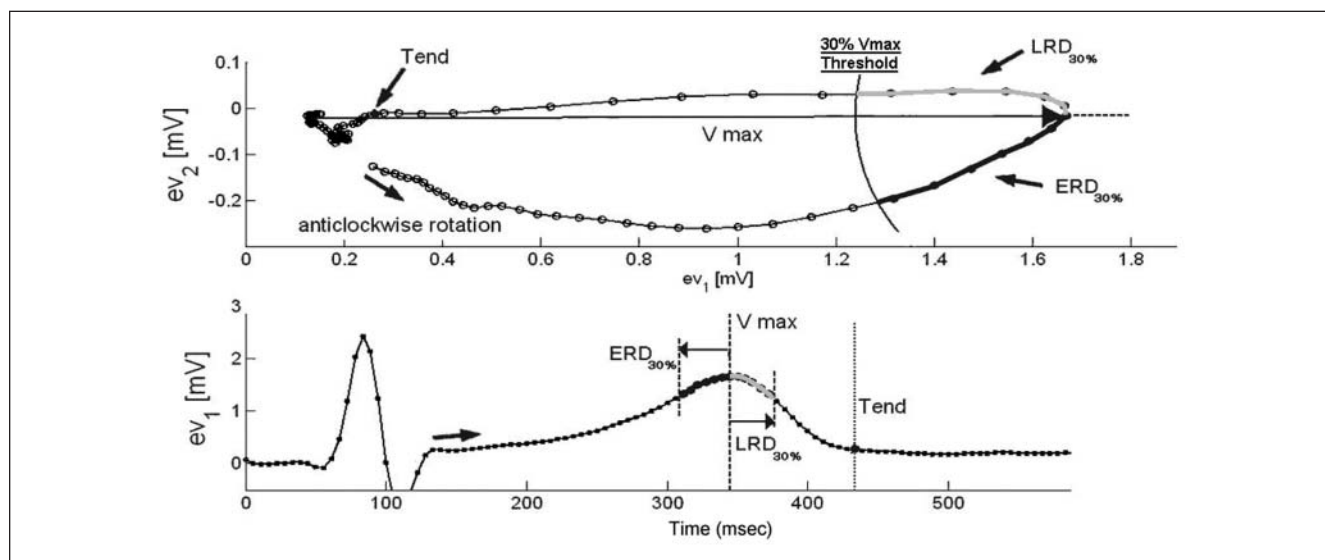


Figure 1. Description of the vectocardiographic measurements of the early (ERD) and late (LRD) repolarization measurement. The figure describes  $ERD_{30\%}$  and  $LRD_{30\%}$ , with 30% representing the threshold used for identifying the length of these intervals from the T loop (upper panel) and its corresponding intervals on the first eigenvector (lower panel). ERD encompasses an interval spreading toward the QRS complex, whereas LRD encompasses an interval toward the end of the T-wave.

### QT Interval Measurements From the Scalar Electrocardiograms

The computer-based end of the T wave was visually checked by trained technicians and manually adjusted using the on-screen caliper available in the COMPAS software, if the automatic algorithm failed to correctly identify the end of the T wave (semi-computerized method). The QT interval measurements were done in 3 cardiac beats in sinus rhythm from lead V5 (or II), and the median value from these 3 measures was computed. We report both the scalar computerized and semi-computerized QT interval measurements expressed in milliseconds. Recently, Liu et al<sup>9</sup> reported the presence of an increased T peak to T end interval (TpTe)/QT ratio prior to the development of TdP in a rabbit wedge preparation. This novel parameter was included in our analysis to investigate its interest when measured from human surface ECGs.

### T Loop Measurements

In our analysis, the repolarization interval (RI) is defined between the J point and the point located 220 ms before the next R peak. The determination of the J point was based on an algorithm developed by Zong et al.<sup>15</sup> This ensures that (1) the analysis encompasses all components of the ventricular

repolarization signal, and (2) it is independent from the determination of the end of the T wave. Such approach requires that the patients remain at rest during the ECG recording to avoid high heart rates (ie, short RR intervals in which the T wave would be encompassed 220 ms prior to the next R peak).

The method is based on the singular value decomposition (SVD) of the RIs from the 12-lead signals. SVD is used to reduce the dimension of the ECG lead systems from 12 leads to 2 leads.<sup>16</sup> We refer to the resulting 2 leads as the eigenvectors 1 ( $ev_1$ ) and 2 ( $ev_2$ ). We measured the QT, QT<sub>apex</sub>, and the TpTe intervals (TpTe = QT - QT<sub>apex</sub>) from  $ev_1$ . The apex and the end of the T wave were identified in a fully computerized manner using the method described above for scalar measurements. We called the T loop the representation of the RI in the 2-dimensional space, defined by  $ev_1$  and  $ev_2$  (upper panel of Figure 1). The vector describing the T loop path across time is the repolarization vector.

The early repolarization duration (ERD) and the late repolarization duration (LRD) are measurements of interval duration based on the T loop. The starting point of these intervals is the time at which the length of the repolarization vector is maximized ( $V_{max}$  in the upper panel of Figure 1). The ending point of these intervals is delimited by a circle of diameter equal to 30% (for  $ERD_{30\%}$  and  $LRD_{30\%}$ ) of

$V_{\max}$  (Figure 1). Consequently, these parameters measure the time needed for the heart vector to vary from its maximum length to a time point corresponding to a 30% reduction of its maximum length during the repolarization process.  $LRD_{\%}$  is a measure toward the end of the RI, and  $ERD_{\%}$  is directed toward the J point (see Figure 1, lower panel). The duration of these time intervals increases when the heart vector slows down or/and the roundness of the T loop increases. Consequently, these parameters measure repolarization duration (reflected in the velocity of the heart vector) and the repolarization heterogeneity (reflected in the path of the heart vector or T loop morphology).

### Heart Rate Correction

All repolarization measurements were heart rate corrected using the pooled technique. A linear regression analysis was used to model the relationship between repolarization measurements and RR intervals during baseline periods. The slope ( $\beta$ ) characterizing this relationship was used to correct the repolarization measurements such as  $QT_c = QT + \beta(1 - RR)$  for the QT interval. The same heart rate correction technique was applied to all other measurements.

### QT Variability

The instability of the repolarization was estimated using the median absolute deviation (MAD) of the beat-to-beat measurements of the semi-computerized QT and QT<sub>apex</sub> parameters after heart rate correction based on the pooled formula. To further control for the effect of RR variation, we divided these MAD values by the MAD of the RR intervals ( $MAD_{QT_c}/MAD_{RR}$ ).

### Heart Rate Variability

The heart rate variability (HRV) was estimated from the 5-minute recordings using an autoregressive method. The normalized high- (HF<sub>norm</sub>) and low-frequency (LF<sub>norm</sub>) components, expressed in percentages, were computed using the SuperECG software (Mortara Instrument). The definition of the frequency bands for the HF and LF components was recommended by the European Task Force.<sup>17</sup> The standard deviation from normal-to-normal intervals (SDNN) was also computed in milliseconds.

### Statistical Analysis

Differences between groups were expressed as mean  $\pm$  standard deviation. The analysis of correlation between values of various parameters was based on Spearman rank correlation, and we report its associated coefficients ( $\rho$ ). *P* values less than or equal to .05 were considered statistically significant. We used logistic regression models to describe the association between baseline ECG measures and the level of drug-induced ECG changes. When we investigated the presence of a history of TdP as the primary endpoint, binary logistic regression models were used, and both the best subsets regression procedure and the stepwise procedure were used to select the optimal models. The statistical analyses were done using SAS (SAS Institute, Cary, North Carolina).

## RESULTS

### Study Population

The clinical characteristics of the study population are provided in Table I. The average ages of the populations were not significantly different between the 2 groups:  $59 \pm 13$  years versus  $61 \pm 12$  years. The number of women was slightly higher ( $n = 12$ ) in the group of individuals without TdP than in the group with TdP ( $n = 9$ ). Presence of a history of myocardial infarction, coronary artery disease, and hypertension was similar between the study groups. There were several patients with a history of atrial fibrillation in both groups (+TdP:  $n = 11$  and -TdP:  $n = 17$ ,  $P < .05$ ). One of the patients had atrial fibrillation during the ECG recording. This ECG was removed from the analysis, resulting in a group of 16 patients with a history of TdP and 17 individuals free of such history.

The group of individuals with a history of drug-induced TdP has been reported using a heterogeneous list of medications. Seven of the patients had sotalol-induced TdP. None of the patients in the study experienced episodes of TdP during the sotalol challenge, and none of them carried a mutation linked to the major congenital forms of the LQTS.

Tables II and III provide the ECG-based parameters across populations for the baseline recordings and for the sotalol-induced changes, respectively. PR and QRS durations were not significantly different between groups at baseline and after drug. As shown in Table III, the RR intervals were significantly

**Table I** Description of Clinical Factors of the Study Population

AF	CAD	MI	EF, %	Drug Inducing TdP
<b>Group With History of Torsades de Pointes</b>				
Y	N	N		Sotalol
Y	N	N		Ciprofloxacin
Y	N	N		Sumatriptane
N	N	N		Erythromycin/roxythromycin
Y	N	N	59	Sotalol
Y	Y	Y	30	Amiodarone
Y	Y	Y	45	Sotalol
N	N	N		Bisacodyl
N	N	N	59	Sotalol
Y	Y	Y	56	Erythromycin
Y	N	N		Sotalol
Y	N	N	29	Sotalol
N	N	N		Imipramin
	N	N		Cipramil
Y	N	N	59	Amiodarone
Y	N	N		Sotalol, cipramil, furosemide
N	N	N	30	Clarithromycin
<b>Group Without History of Torsades de Pointes</b>				
Y	N	N		
Y	N	N		
Y	N	N	69	
N	Y	Y		
Y	N	N		
Y	N	N		
Y	N	N		
Y	N	N		
Y	N	N		
Y	Y	N		
Y	N	N		
Y	N	N		
Y	N	N		
Y	Y	N	67	
Y	N	N		
Y	N	N		
Y	N	N		

Y/N, yes/no; EF, left ventricular ejection fraction; CAD, coronary artery disease; MI, myocardial infarction; HT, history of hypertension; AF, history of atrial fibrillation; TdP, Torsades de Pointes.

longer after sotalol (+TdP:  $201 \pm 101$  ms and -TdP:  $175 \pm 98$  ms,  $P < .05$ ), but the bradycardic effect of the drug was not different between groups ( $P = .45$ ).

### Baseline Duration, Heterogeneity, and Instability of Repolarization

*Scalar measurements.* In comparison to the scalar QTc interval measurements, we found similar

results using the semi- or fully computerized method in baseline conditions (Table II). The group of +TdP patients had a longer QT interval duration ( $\sim 25$  ms) than -TdP patients. We identified 6 patients with a QTc duration above the gender-specific threshold for LQTS (QTc  $>480$  ms in women and QTc  $>470$  ms in men). One of them was a woman from the control group (-TdP); the remaining ones were from the +TdP group and included 3 men and 2 women.

*Vectorial measurements.* At baseline, the vectorial QT measurements (from  $ev_1$ ) were slightly longer than the scalar QT intervals, but the difference between the study groups remained consistent (26 ms). According to the vectorial parameters, this prolongation was localized within the early part of the repolarization segment, as shown by ERD<sub>30%</sub> and ERD<sub>50%</sub>. ERD<sub>30%</sub> was 9 ms longer in the +TdP group ( $P = .02$ ), and this prolongation reached 14 ms with ERD<sub>50%</sub> ( $P = .03$ ). Interestingly, this delay in the early phase of the repolarization segment was not captured by the QT<sub>apex</sub> interval (from  $ev_1$ ), suggesting that the morphology of the T loop (ventricular heterogeneity) primarily drives this delay.

Our investigation of QT variability reveals a trend toward larger variability in baseline ECGs of +TdP patients, but this difference did not reach statistical significance.

### Sotalol-Induced Prolongation, Heterogeneity, and Instability of Repolarization

*Scalar measurements.* Sotalol is associated with strong prolongation of the QTc interval duration, and this was true for the 2 groups (+TdP:  $85 \pm 42$  and -TdP:  $65 \pm 47$  ms). These changes were statistically different from zero ( $P < .0001$ ) but not statistically different between groups ( $P = .22$ ) when considering single lead-based measurements. Similar results were found using the scalar computerized technique (+TdP:  $63 \pm 57$  and -TdP:  $56 \pm 41$  ms,  $P = .70$ ).

The ratio of the terminal part of the T wave to the QTc interval was not significantly different between groups.

*Vectorial measurements.* There was a significant sotalol-induced QTc and QTc apex prolongation ( $P < .01$ ) within the 2 study groups. It is noteworthy that QTc measured from  $ev_1$  did reveal statistically significant prolongation in the +TdP group ( $75 \pm 44$  vs  $37 \pm 26$  ms,  $P = .008$ ). This observation is consistent with Kaab and coworkers' results<sup>12</sup> evidencing

**Table II** Description of Baseline Values of Electrocardiographic Parameters

	Baseline (Absolute Values)		P Values
	-TdP (n = 17)	+TdP (n = 16)	
Scalar measurements <sup>a</sup>			
RR	925 ± 162	922 ± 142	.96
PR	161 ± 28	153 ± 27	.45
QRS	97 ± 15	95 ± 11	.68
QTc, semi-computerized	<b>433 ± 34</b>	<b>458 ± 34</b>	<b>.04</b>
QTc, computerized	<b>432 ± 33</b>	<b>461 ± 43</b>	<b>.04</b>
TpTe/QTc (NU)	0.25 ± 0.06	0.23 ± 0.05	.60
Computerized vectocardiographic measurements <sup>a</sup>			
QTc apex	350 ± 19	358 ± 23	.30
QTc	<b>444 ± 28</b>	<b>470 ± 38</b>	<b>.03</b>
TpTe	94 ± 13	112 ± 48	.79
ERD <sub>30%</sub>	<b>35 ± 8</b>	<b>44 ± 13</b>	<b>.02</b>
ERD <sub>50%</sub>	<b>58 ± 13</b>	<b>72 ± 22</b>	<b>.03</b>
ERD <sub>70%</sub>	92 ± 32	114 ± 40	.10
LRD <sub>30%</sub>	28 ± 5	35 ± 18	.22
LRD <sub>50%</sub>	44 ± 5	56 ± 32	.36
LRD <sub>70%</sub>	69 ± 11	89 ± 43	.23
QT variability			
MAD <sub>QTc</sub> /MAD <sub>RR</sub>	0.41 ± 0.17	0.90 ± 0.89	.30
MAD <sub>QTc apex</sub> /MAD <sub>RR</sub>	0.23 ± 0.08	0.50 ± 0.63	.47
HRV measurements			
SDNN, ms	44.5 ± 14.8	49.8 ± 20.8	.41
HF norm, %	45.8 ± 8.8	44.5 ± 7.8	.66
LF norm, %	29.0 ± 5.7	28.4 ± 9.1	.82

-TdP, patients without a history of TdP; +TdP, patients with a history of TdP; TpTe, T peak to T end interval in lead II; ERD, early repolarization duration; LRD, late repolarization duration (for definition of the ERD and LRD parameters, see text); HF, high frequency; LF, low frequency; MAD, median absolute deviation; HRV, heart rate variability; SDNN, standard deviation from normal-to-normal intervals; TdP, Torsades de Pointes. Values associated with  $P < .05$  are in bold. NU, no unit.

a. These measurements are corrected using the pooled formula and expressed in milliseconds.

significantly larger sotalol-induced QT prolongation between patients with and without a history of TdP using the maximum QT interval from all available leads. More interestingly, sotalol significantly prolonged the late part of the repolarization in the group of patients with a history of TdP: their TpTe interval prolongation was longer ( $23 \pm 27$  vs  $4 \pm 12$  ms,  $P = .02$ ), and their LRD<sub>70%</sub> (and LRD<sub>50%</sub>; see Table III) values were more prolonged ( $20 \pm 29$  vs  $2 \pm 14$  ms,  $P = .04$ ).

No significant changes in SDNN values and LF norm values were found after sotalol in any of the study groups. But the high-frequency norm revealed a trend toward increased parasympathetic innervations in the group of patients with a history of TdP (-TdP:  $6.7\% \pm 11.7\%$  vs +TdP:  $14.5\% \pm 8.1\%$ ,  $P = .05$ ).

The variability of the QTc and QTc apex interval durations, adjusted for heart rate, was measured using the ratio of MAD<sub>QTc</sub> to MAD<sub>RR</sub>. No difference in

levels of QT variability was found in ECGs recorded for sotalol (see Table III).

### Characterizing Patients With a History of Torsades de Pointes

Binary logistic regressions were implemented to find which baseline information could help predict the presence of a history of TdP in a multivariate fashion. The QTc, QTc apex, TpTe, TpTe/QTc, MAD<sub>QTc</sub>/MAD<sub>RR</sub>, ERD<sub>x%</sub>, and LRD<sub>x%</sub> were included in the design. Based on both stepwise and best subsets, the model revealed that ERD<sub>30%</sub> was the strongest predictor of a history of TdP. For each incremental 1-ms duration of ERD<sub>30%</sub>, there was a 14.2% increased odds of having a history of TdP ( $P = .016$ ). The second selected parameter was MAD<sub>QTc</sub>/MAD<sub>RR</sub> associated with a 41% increase for each 0.1 increase in value ( $P = .066$ ). Baseline QTc or TpTe intervals did

**Table III** Description of Sotalol-Induced Changes in Values of Electrocardiographic Parameters

	Sotalol Challenge (Sotalol-Induced Changes)		
	-TdP (n = 17)	+TdP (n = 16)	P Values
Scalar measurements <sup>a</sup>			
RR	175 ± 98*	201 ± 101*	.45
PR	3 ± 27	5 ± 22	.61
QRS	0 ± 9	3 ± 13	.85
QTc, semi-computerized	65 ± 47*	85 ± 42*	.22
QTc, computerized	56 ± 41*	63 ± 57*	.70
TpTe/QTc (NU)	-0.013 ± 0.039	0.023 ± 0.068	.18
Computerized vectocardiographic measurements <sup>a</sup>			
QTc apex	34 ± 23*	52 ± 40*	.13
QTc	<b>37 ± 26*</b>	<b>75 ± 44*</b>	<b>.008</b>
TpTe	<b>4 ± 12</b>	<b>23 ± 27*</b>	<b>.02</b>
ERD <sub>30%</sub>	15 ± 19*	12 ± 20*	.68
ERD <sub>50%</sub>	24 ± 30*	26 ± 27*	.84
ERD <sub>70%</sub>	30 ± 44*	32 ± 51*	.89
LRD <sub>30%</sub>	6 ± 10	6 ± 15	.31
LRD <sub>50%</sub>	<b>6 ± 10*</b>	<b>20 ± 27*</b>	<b>.02</b>
LRD <sub>70%</sub>	<b>2 ± 14</b>	<b>20 ± 29*</b>	<b>.04</b>
QT variability			
MAD <sub>QTc</sub> /MAD <sub>RR</sub>	0.23 ± 0.32	0.33 ± 0.63	.55
MAD <sub>QTc apex</sub> /MAD <sub>RR</sub>	0.07 ± 0.17	0.11 ± 0.54	.63
HRV measurements			
SDNN, ms	7.6 ± 24.5	-2.8 ± 22.1	.24
HF norm, %	<b>6.7 ± 11.7</b>	<b>14.5 ± 8.1*</b>	<b>.05</b>
LF norm, %	1.9 ± 6.1	-1.1 ± 8.4	.40

-TdP, patients without a history of TdP; +TdP, patients with a history of TdP; TpTe, T peak to T end interval in lead II; ERD, early repolarization duration; LRD, late repolarization duration (for definition of the ERD and LRD parameters, see text); HF, high frequency; LF, low frequency; MAD, median absolute deviation; HRV, heart rate variability; SDNN, standard deviation from normal-to-normal intervals; TdP, Torsades de Pointes. Values associated with  $P < .05$  are in bold. Testing if the average is different from 0: \* $P < .01$ . NU, no unit.

a. These measurements are corrected using the pooled formula and expressed in milliseconds.

not contribute to the model despite the presence of 5 patients with a prolonged QTc interval at baseline in the +TdP group.

A second logistic model was implemented considering the sotalol-induced TpTe interval prolongation as a primary continuous endpoint and baseline ECG measurements as covariates. Again, both ERD<sub>30%</sub> and MAD<sub>QTc</sub>/MAD<sub>RR</sub> were selected as independent predictors of this continuous endpoint:

For each 1-ms increment of ERD<sub>30%</sub> at baseline, there was a 1.8-ms increment in TpTe interval value with a strong statistical significance ( $P = .0002$ ). A univariate regression analysis between ERD<sub>30%</sub> and sotalol-induced prolongation of TpTe was significant ( $r^2 = 31\%$ ,  $P < .0001$ ).

For each increment of 0.1 units of the MAD<sub>QTc</sub>/MAD<sub>RR</sub> value, there was a 1.8-ms increment in the TpTe interval on sotalol ( $P = .01$ ).

None of the other ECG measurements entered the model—that is, neither baseline QT interval duration nor baseline TpTe interval contributed to the prediction of sotalol-induced TpTe prolongation.

On the basis of these results, we report in the upper panel of Figure 2 the scatterplots for ERD<sub>30%</sub> and QT variability values in the 2 study groups at baseline. Using a maximum value of ERD<sub>30%</sub> (>47 ms) and MAD<sub>QTc</sub>/MAD<sub>RR</sub> (>0.72) in patients without a history of TdP, one can separate the 2 groups with 100% specificity and 69% sensitivity. The 6 individuals presented prolonged QT intervals on their baseline ECGs (LQTS) based on the following clinical criterion: QTc >480 ms in women and QTc >470 ms in men (see Figure 2). One may note that 7 patients without clinically identifiable LQTS were detected by our novel parameters. Among them, 3 patients have borderline QTc (450 ms > QTc >470 ms),

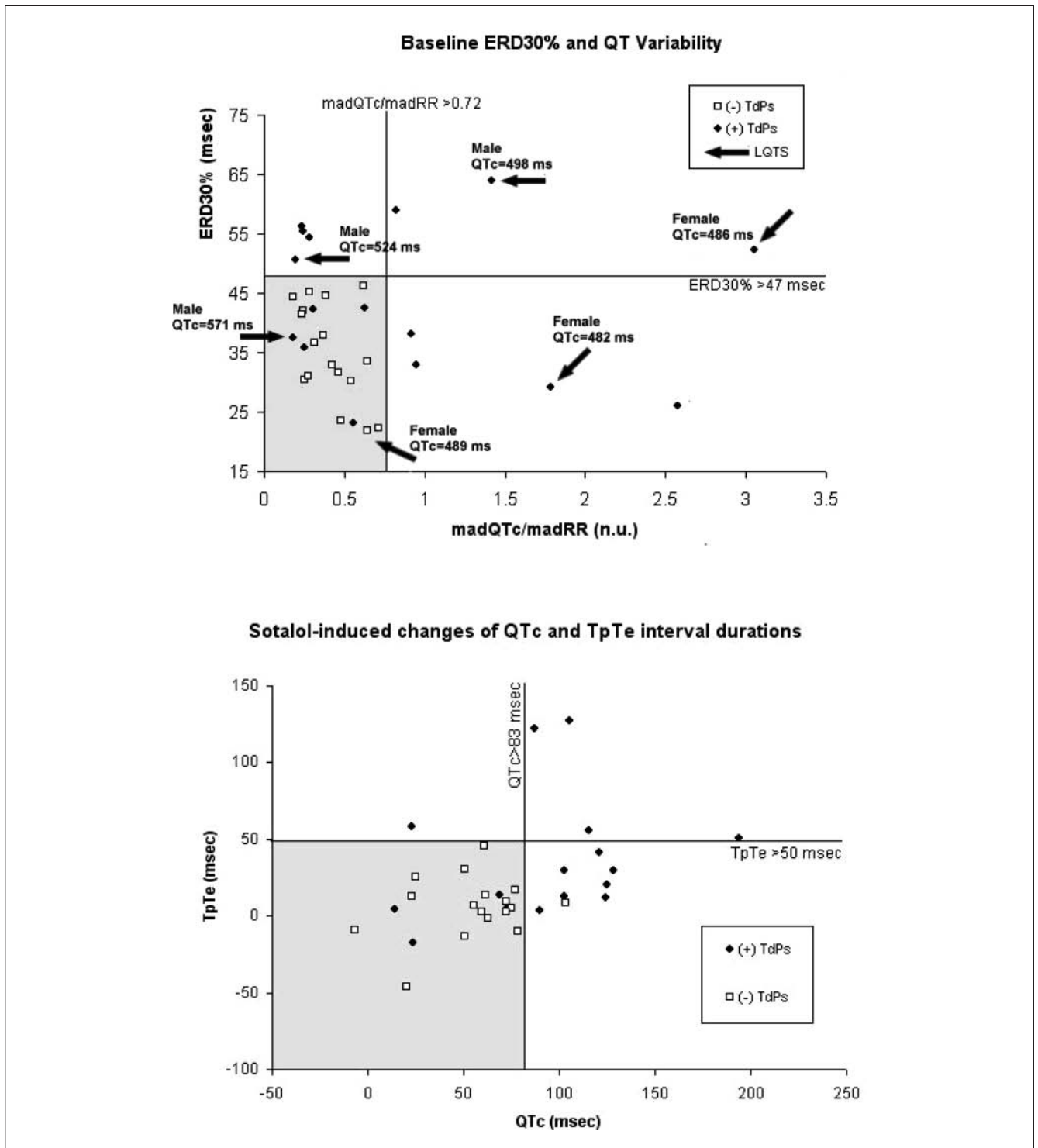


Figure 2. Distribution of heart rate–corrected values for  $ERD_{30\%}$  and the values of QT variability (upper panel) in baseline electrocardiograms (ECGs) for our study populations marking the patients with long QT interval duration (based on gender-specific criteria of the long QT syndrome). The sotalol-induced changes of TpTe and QTc interval (computerized) are reported in the lower panel. The gray areas in both panels represent the range of values in which most patients without history of Torsades de Pointes (TdP) are located. The vertical and horizontal lines define the values of the parameter thresholds.

and 4 have normal QTc interval duration. Consequently, using a criterion based on QTc >450 ms to identify patients with increased risk would provide a sensitivity of 50% and a specificity of 76%. This univariate analysis confirms our observations from the multivariate analysis that our novel ECG parameters are bringing complementary information to QT prolongation.

Figure 2 also provides the scatterplot of values of sotalol-induced changes for TpTe and QTc intervals. We defined thresholds for maximizing the separation between the 2 groups as the sotalol-induced changes in TpTe >50 ms and in QTc >83 ms, and the groups can be separated with 94% specificity and 75% sensitivity based on these thresholds.

## DISCUSSION

We report the analysis of ventricular repolarization duration, heterogeneity, and instability in a group of individuals with and without a history of drug-induced TdP. We investigated ECG abnormalities that could be linked to arrhythmogenic factors contributing to trigger and maintain drug-induced TdP. Repolarization heterogeneity and instability were assessed from surface ECGs based on the T loop morphology (ERD and LRD parameters) and QT variability. The assessment of reverse use dependency of sotalol using QT/RR modeling was not included in our analysis because the ECG recordings were too short to reliably assess the QT/RR relationship.<sup>18</sup>

The baseline ECGs of patients with a history of TdP revealed more pronounced repolarization abnormalities in comparison to the ECGs of patients without such history. This increased repolarization variability measured from baseline ECGs was not significantly different between the 2 study groups, but the multivariate analysis suggested that this variability contributed to better classify these groups. Such observation is consistent with the beat-to-beat variability of QT described in the study reported by Hinterseer et al.<sup>19</sup> This instability of repolarization is 1 of 3 components of the TriAD concept, and its proarrhythmic role has been documented in several clinical studies that have reported their independent predicting value for appropriate implantable cardio-defibrillator therapy in postinfarction patients.<sup>20,21</sup>

At baseline, our investigation revealed that the repolarization delay was prominently located in the early part of the T wave prior to its apex. Thus, a large set of patients with a history of drug-induced

TdP had a specific repolarization profile similar to the one we observed in ECGs of healthy participants on moxifloxacin—namely, changes in morphology of the T wave prior to the T wave apex.<sup>16</sup> It is noteworthy that the T wave from LQT2 patients with borderline QTc interval duration (390-440 ms) also shows an abnormal early portion of the T wave (quantified using the left slope of the T wave). This information helps to better identify patients carrying the KCNH2 mutation from noncarrier family members.<sup>14</sup> In this study group, patients did not carry any of the major LQTS mutations, but our observations might also reveal the presence of a reduced repolarization reserve. Indeed, unrecognized repolarization modulators could be present such as nondocumented drugs, underlying cardiac disease, and predisposing genetic factors (nonidentified congenital long QT syndrome).

When patients with a history of TdP are exposed to the torsadogenic compound sotalol, the repolarization abnormalities are not limited to the early part of the T wave but extend to the late portion of the T wave. Our results show that the late part of the T wave, measured either by the TpTe interval or the LRD<sub>x%</sub> parameters, is more significantly prolonged during an infusion of sotalol in patients with a history of TdP than in patients without such history. In human studies, Smetana et al<sup>22</sup> investigated the TpTe interval duration in the European Myocardial Infarction Amiodarone Trial (EMIAT) population, comparing the length of this interval between patients who died or did not die of cardiac arrhythmic events. The results suggested a significant prolongation of the TpTe interval in patients who died in the placebo group ( $71 \pm 3$  vs  $66 \pm 1$  ms,  $P = .04$ ). Interestingly, this difference was not found in the group of patients on amiodarone (both groups had long TpTe intervals of  $79 \pm 6$  vs  $73.2 \pm 2$  ms,  $P = .17$ ). The ratio between TpTe and QT interval was not longer in patients with a history of TdP. This observation is not consistent with Liu et al's work<sup>9</sup> reporting increased values of this ratio prior to the occurrence of TdP in a rabbit model.

Our study suggests that the prolongation of the QT intervals at baseline and on sotalol in patients with a history of TdP is associated with an unevenly distributed delay across the repolarization interval. These observations fit the arrhythmogenic concept, enhancing the role of the TpTe interval prolongation as an important proarrhythmic factor.<sup>9,10</sup> Animal and clinical investigations have emphasized that a prolongation of the QT interval might be more or less

malignant according to the location of the abnormality inside the T wave in erythromycin-induced LQTS, in arterially perfused wedges from the canine left ventricle,<sup>23</sup> and in cases of Brugada syndrome.<sup>24</sup>

Finally, a univariate analysis of the correlation between repolarization parameters at baseline and on sotalol revealed that baseline ERD<sub>30%</sub> values were significantly correlated with sotalol-induced TpTe prolongation ( $r^2 = 31\%$ ,  $P < .0001$ ). Our logistic models confirm this strong relationship and suggest that a prolongation of the late and the early part of the repolarization signal are not independent. The mechanism underlying this dependency remains to be elucidated.

The values of the time domain HRV parameter and of the high-frequency components were very similar to the HRV indices reported in normal participants for short-term recordings using an autoregressive method.<sup>25</sup> But our study groups were characterized by a vagally driven regulation of the heart rate at baseline. A parasympathetically driven regulation is known to increase QT interval duration: Viitasalo and Karjalainen<sup>26</sup> have shown an 18-ms QT prolongation during night compared with day recordings for the same level of heart rate (60 bpm). The prolongation of the QT interval under vagal influence has been confirmed by Bexton et al,<sup>27</sup> who investigated the influence of the autonomic nervous system (ANS) on the QT interval. For these reasons, we believe it is important to combine information about the repolarization changes and the presence of an “atypical” regulation of the heart by the ANS. In our study, the group of patients with a history of TdP was associated with a statistically significant sotalol-induced increased parasympathetic regulation of the heart rate that could mean that these patients might have an increased sensibility to a beta-adrenergic blocking property of dl-sotalol, enhancing their increased propensity to repolarization delay and to ventricular heterogeneity.

### Limitations of the Study

The size of the study population was rather small but contained a large set of ECG recordings from patients with history of TdP. As far as we know, it is the largest set of digital ECGs in a group of patients with a history of such rare arrhythmias. The logistic model developed in our study has a limited value as a predictive tool until it is validated on an independent set of data.

In this study, we used individuals with prior documented TdP induced by various types of QT-prolonging drugs. We do not have information about drug level and triggering events in these patients. Also, none of the patients in the group with a history of TdP had an episode of TdP while on sotalol. Even if one does not fully understand the mechanisms involved in the triggering of drug-induced TdP, one could speculate that if sotalol strongly impaired the repolarization process, it might not set up all components needed for triggering TdP in our patients with a torsadogenic predisposition. It has been shown in clinical studies of patients with the congenital long QT syndrome that there are crucial environmental factors known to trigger the occurrence of cardiac arrhythmias. Schwartz et al<sup>28</sup> observed that in LQT2 patients (patients with reduced  $I_{kr}$  kinetics), most cardiac events occur following an emotional stress event (abrupt neurally mediated release of norepinephrine), whereas LQT1 patients have events during exercise. In LQT1 patients, the risk for arrhythmic events is increased when the protective effect of the  $I_{ks}$  current does not “kick in” at a high heart rate. Such cardiac stress events were not included in our experiment but could have been crucial triggering events of TdP in our positive study group.

Finally, Hong et al<sup>29</sup> suggested that patients with atrial fibrillation may have a shortening of the QT interval. The KCNH3-K897T polymorphism associated with atrial fibrillation<sup>30</sup> is suggested to be also associated with QT shortening based on large cohorts of patients from the MONICA, KORA, and Framingham Heart Studies.<sup>31</sup> One must acknowledge that our study groups are both primarily constituted by patients with a history of atrial fibrillation: all -TdP patients and 11 of 16 patients in the +TdP group.

### Conclusion

It is important for clinicians and for pharmaceutical companies to be able to assess the level of predisposition to TdP of an individual. When comparing the ECGs from patients with and without a history of TdP, our results suggest that patients with a history of drug-induced TdP have specific T wave morphologies on their baseline ECGs. When challenged by sotalol, the patients with a history of TdP have a significantly longer late portion of the T wave than the patients without such history. We believe this information could help optimize therapeutic

strategies for cardiologists and improve the design of studies for drug safety assessment.

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