

ORIGINAL RESEARCH

# Short-Term Variability of the QT Interval Can be Used for the Prediction of Imminent Ventricular Arrhythmias in Patients With Primary Prophylactic Implantable Cardioverter Defibrillators

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**BACKGROUND:** Short-term variability of the QT interval ( $STV_{QT}$ ) has been proposed as a novel electrophysiological marker for the prediction of imminent ventricular arrhythmias in animal models. Our aim is to study whether  $STV_{QT}$  can predict imminent ventricular arrhythmias in patients.

**METHODS AND RESULTS:** In 2331 patients with primary prophylactic implantable cardioverter defibrillators, 24-hour ECG Holter recordings were obtained as part of the EU-CERT-ICD (European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators) study. ECG Holter recordings showing ventricular arrhythmias of >4 consecutive complexes were selected for the arrhythmic groups ( $n=170$ ), whereas a control group was randomly selected from the remaining Holter recordings ( $n=37$ ).  $STV_{QT}$  was determined from 31 beats with fiducial segment averaging and calculated as  $\sum |D_{n+1} - D_n| / (30 \times \sqrt{2})$ , where  $D_n$  represents the QT interval.  $STV_{QT}$  was determined before the ventricular arrhythmia or 8:00 AM in the control group and between 1:30 and 4:30 AM as baseline.  $STV_{QT}$  at baseline was  $0.84 \pm 0.47$  ms and increased to  $1.18 \pm 0.74$  ms ( $P < 0.05$ ) before the ventricular arrhythmia, whereas the  $STV_{QT}$  in the control group remained unchanged. The arrhythmic patients were divided into three groups based on the severity of the arrhythmia: (1) nonsustained ventricular arrhythmia ( $n=32$ ), (2) nonsustained ventricular tachycardia ( $n=134$ ), (3) sustained ventricular tachycardia ( $n=4$ ).  $STV_{QT}$  increased before nonsustained ventricular arrhythmia, nonsustained ventricular tachycardia, and sustained ventricular tachycardia from  $0.80 \pm 0.43$  ms to  $1.18 \pm 0.78$  ms ( $P < 0.05$ ), from  $0.90 \pm 0.49$  ms to  $1.14 \pm 0.70$  ms ( $P < 0.05$ ), and from  $1.05 \pm 0.22$  ms to  $2.33 \pm 1.25$  ms ( $P < 0.05$ ). This rise in  $STV_{QT}$  was significantly higher in sustained ventricular tachycardia compared with nonsustained ventricular arrhythmia ( $+1.28 \pm 1.05$  ms versus  $+0.24 \pm 0.57$  ms [ $P < 0.05$ ]) and compared with nonsustained ventricular arrhythmia ( $+0.34 \pm 0.87$  ms [ $P < 0.05$ ]).

**CONCLUSIONS:**  $STV_{QT}$  increases before imminent ventricular arrhythmias in patients, and the extent of the increase is associated with the severity of the ventricular arrhythmia.

**Key Words:** short-term variability of repolarization ■ ventricular arrhythmia ■ ventricular tachycardia

**T**reatment of ventricular arrhythmias and prevention of sudden cardiac death (SCD) rapidly evolved in the past century, and innovations continuously contribute to further improvement. Introduction of the

implantable cardioverter defibrillator (ICD) reduced the mortality rate in patients with a high risk for SCD.<sup>1-3</sup> Nevertheless, SCD remains an important healthcare concern, and research about underlying mechanisms

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## CLINICAL PERSPECTIVE

### What Is New?

- In patients with primary prophylactic implantable cardioverter defibrillators, an increase in temporal dispersion of repolarization, quantified as short-term variability of the QT interval, precedes ventricular arrhythmias.
- The extent of the increase in short-term variability of the QT interval is associated with the severity of the ventricular arrhythmia.

### What Are the Clinical Implications?

- Temporal dispersion of repolarization is a promising parameter for monitoring imminent ventricular arrhythmias.

## Nonstandard Abbreviations and Acronyms

<b>ΔSTV<sub>QT</sub></b>	STVQT before ventricular arrhythmia minus STV <sub>QT</sub> at baseline
<b>EU-CERT-ICD</b>	European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators
<b>nsVA</b>	nonsustained ventricular arrhythmia
<b>nsVT</b>	nonsustained ventricular tachycardia
<b>SCD</b>	sudden cardiac death
<b>STV</b>	short-term variability
<b>STV<sub>QT</sub></b>	short-term variability of the QT interval

and novel treatments is ongoing.<sup>4</sup> Temporal dispersion of repolarization, quantified as short-term variability (STV), has been identified as a promising marker for arrhythmic risk monitoring. In animal models, STV at baseline discriminated between subjects that developed ventricular arrhythmias or SCD in the long term.<sup>5–7</sup> Similar results were obtained in patients with acquired<sup>8</sup> or congenital<sup>9</sup> long-QT syndrome, patients with nonischemic heart failure,<sup>10</sup> and patients with structural heart disease,<sup>11</sup> where an elevated STV at baseline was associated with patients with a history of ventricular arrhythmias or the occurrence of ventricular arrhythmias during follow-up. A novel application of STV, being the ability to predict imminent ventricular arrhythmias, has also been studied preclinically. In animal studies, STV increases abruptly before ventricular

arrhythmias, whereas it remains stable in the absence of arrhythmic events.<sup>6,12,13</sup> Moreover, STV is a suitable parameter to guide preventive therapy to avert the immediate (re)occurrence of ventricular arrhythmias.<sup>14</sup> We aim to investigate whether STV of the QT interval (STV<sub>QT</sub>) also increases before ventricular arrhythmias in patients and could therefore be used to predict imminent ventricular arrhythmias in a clinical setting.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study Design

The EU-CERT-ICD (European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators) is a prospective multicenter, observational study.<sup>15</sup> It aims to assess the current clinical value of the ICD in patients with primary prophylaxis and the electrocardiographic parameters at baseline for long-term prediction of all-cause mortality and appropriate ICD shocks. Patients with ischemic and nonischemic cardiomyopathy fulfilling the international treatment guidelines for primary prophylactic ICD implantation were included.<sup>16</sup> The protocol was approved by the institutional review board or ethics committee at each participating hospital and was in compliance with the Declaration of Helsinki. All patients provided written informed consent. A 12-lead Holter ECG (CM 3000-12 BT; Getemed, Teltow, Germany) was recorded at 1 kHz sampling frequency for 24 hours in hospitalized patients before the ICD implantation. Holter recordings showing ventricular arrhythmias of >4 consecutive complexes were selected. A control group was randomly selected from the remaining Holter recordings not fulfilling this criterion.

### Measurement of STV<sub>QT</sub> and other electrophysiological parameters

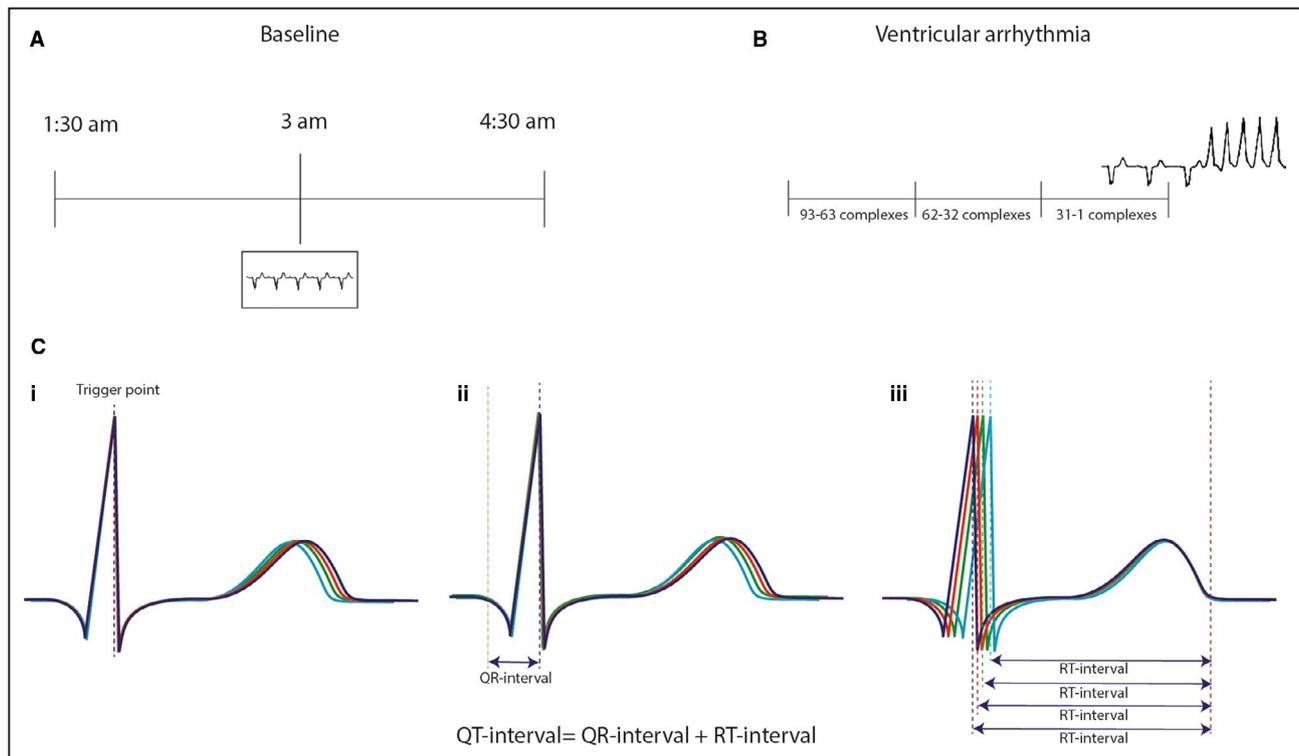
Precordial lead V2 or V3 was selected in each patient based on the morphology of the T-wave. The precordial lead with the highest amplitude and slope at the end of the T-wave was used for the determination of the RR and QT intervals and for the calculation of STV<sub>QT</sub>. QTc was calculated according to the Framingham formula. STV<sub>QT</sub> of 31 consecutive beats was calculated using the formula  $\sum |D_{n+1} - D_n| / (N \times \sqrt{2})$ , where  $D$  represents the determinant of repolarization (in this case the QT interval), and  $N$  represents the number of beats taken into account  $-1$ .<sup>12</sup> The change in STV<sub>QT</sub> between baseline and before ventricular arrhythmia was calculated

as  $\Delta STV_{QT} = STV_{QT}$  of the last 31 complexes before ventricular arrhythmia –  $STV_{QT}$  baseline. All electrophysiological parameters were determined at baseline and before the longest ventricular arrhythmia exhibited by a patient or at 8:00 AM in the control group. The latter time point was chosen because the circadian pattern of  $STV_{QT}$  shows the highest peak at 8:00 AM, especially in patients with a high burden of ventricular ectopy and nonsustained ventricular tachycardia (nsVT).<sup>17</sup> Baseline measurements were performed at 3:00 AM unless a ventricular arrhythmia occurred, then baseline was determined at a time point at least 1.5 hours away from the ventricular arrhythmia but between 1:30 and 4:30 AM (Figure 1A). In addition to the STV of the final 31 complexes preceding the ventricular arrhythmia, STV was also determined on the 32 to 62 and 63 to 93 prior complexes to follow the behavior of STV before the arrhythmic event (Figure 1B). Ventricular and atrial premature complexes together with the preceding and following post-extrasystolic beat were excluded from analysis. We used the method of fiducial segment averaging for the measurement of the QT

interval and calculation of  $STV_{QT}$ .<sup>18</sup> First, all complexes were aligned around a trigger point, in this case the R-peak of the QRS complex by cross-correlating each individual complex with the average of the remainder complexes and then shifting the complex until maximum correlation was obtained (Figure 1CI). Next, the same alignment process was repeated for the 2 other fiducial points, QRS onset and the end of the T-wave, respectively (Figure 1CII and III). Correct alignment was checked visually and adjusted manually where necessary.

## Statistical Analysis

Numeric data are expressed as mean $\pm$ SD unless specified otherwise. One-way analysis of variance (ANOVA) with Tukey correction for multiple comparisons was used for group analyses, and for the comparisons to baseline within a group, 1-way repeated-measures ANOVA with Tukey correction was applied. Group comparisons with both within-subject and between-subject variables were performed with a



**Figure 1. Study methodology.**

Short-term variability of the QT interval was determined twice in every patient: baseline at 3:00 AM unless a ventricular arrhythmia occurred, then the baseline was determined at a time point at least 1.5 hours away from the ventricular arrhythmia but between 1:30 and 4:30 AM (A) and before the ventricular arrhythmia the short-term variability of the QT interval was determined in the last 31 preceding complexes (B). To monitor the behavior of short-term variability of the QT interval before the ventricular arrhythmia, 2 more segments of 31 complexes were used for the determination of short-term variability of the QT interval, namely, the segments of 62 to 32 and 93 to 63 preceding complexes. The method of fiducial segment averaging was applied to determine the QT interval as the sum of the QR interval and the RT interval (C). (I) All complexes were aligned at the R peak as the trigger point. (II) The complexes were aligned at the onset of the QRS complex to determine the QR interval. (III) The complexes were aligned at the T-wave end to determine the RT interval.

2-way ANOVA with Tukey correction for multiple comparisons. Categorical variables were analyzed with a  $\chi^2$  test. Calculations were performed using SPSS (version 26; IBM, Armonk, NY) and Prism (version 8.0; GraphPad Software Inc., La Jolla, CA).  $P < 0.05$  was considered as statistically significant.

## RESULTS

### Study Population

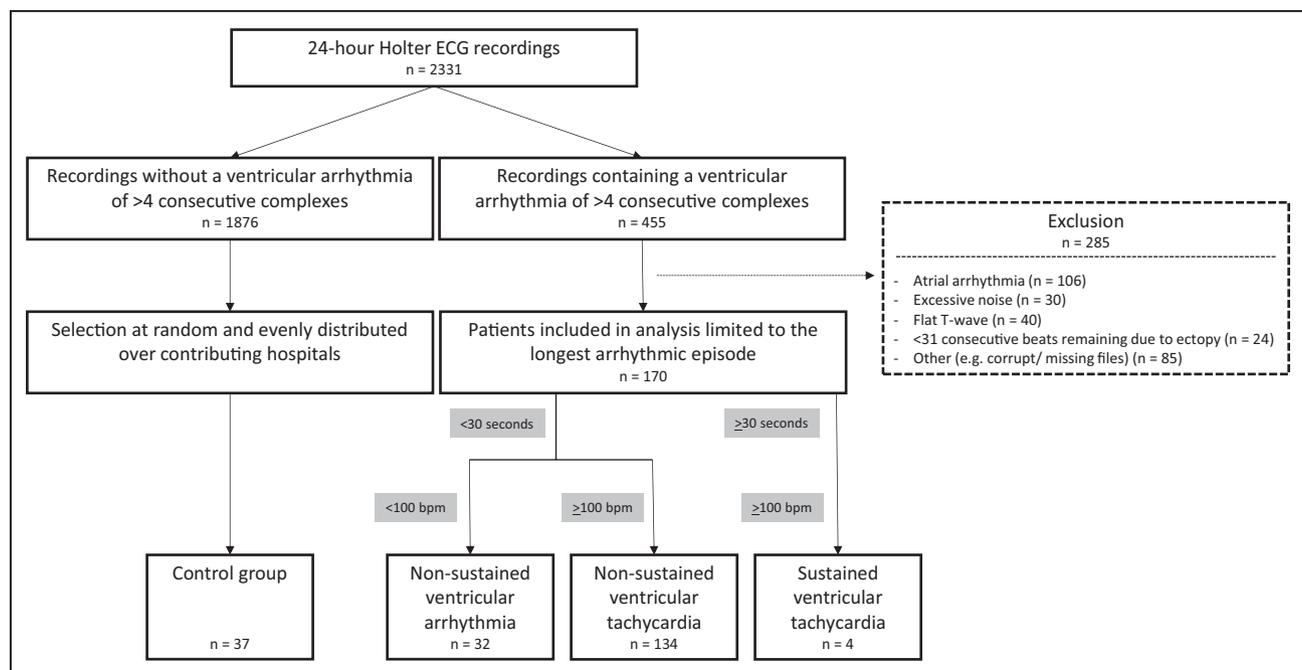
The EU-CERT-ICD study enrolled 2292 patients from May 2014 until August 2018. For this substudy, we screened all the Holter ECG recordings, and 455 patients showed ventricular arrhythmias of >4 consecutive complexes (Figure 2). A total of 285 Holter ECG recordings were excluded from analysis, for example, because of atrial arrhythmias ( $n=106$ ), excessive noise ( $n=30$ ), a flat T-wave ( $n=40$ ), or excessive ectopy resulting in <31 consecutive beats ( $n=24$ ). The remaining 170 Holter ECG recordings were suitable for analysis. A variety of ventricular arrhythmias occurred in the study population; therefore, the patients were divided into 3 groups based on the severity of the arrhythmia. The first group consisted of short-lasting (<30 seconds) ventricular arrhythmias of <100 beats per minute (bpm) defined as nonsustained ventricular arrhythmia (nsVA) ( $n=32$ ). The second group showed short-lasting ventricular tachy-arrhythmias of  $\geq 100$  bpm defined as nsVT

( $n=134$ ). The third group were longer lasting ( $\geq 30$  seconds) ventricular tachy-arrhythmias of  $\geq 100$  bpm defined as sustained ventricular tachycardia (VT) ( $n=4$ ). The control group consisted of 37 patients.

Table 1 shows clinical baseline characteristics of the patients included in the analysis. The VT group was excluded from statistical analysis as a subgroup because of the missing values in an already low number of patients. There were no statistical differences in baseline characteristics between the overall group with ventricular arrhythmias and the control group, nor were there statistical differences between patients with nsVA and nsVT. The mean age of patients with ventricular arrhythmias was  $63 \pm 11$  years and  $60 \pm 12$  years in the control group. The study population was predominantly male, and the majority of the patients had ischemic cardiomyopathy as the leading cardiac disease, with 57% in the overall group with ventricular arrhythmias and 70% in the control group. Medication use was similar in the overall group with ventricular arrhythmias and the control group. In the group with a VT, 33% used  $\beta$ -blockers.

### Arrhythmia Characteristics

Ventricular arrhythmias occurred throughout the day, as illustrated in Figure 3. nsVA tended to occur from late afternoon (5:00 PM) until early morning (7:00 AM), whereas nsVTs were distributed throughout the entire



**Figure 2. Study flow chart.**

The 24-hour Holter ECG recordings containing ventricular arrhythmias with > 4 consecutive beats were selected. After exclusion of recordings rendered unsuitable for analysis, short-term variability of repolarization was measured before the longest arrhythmic episode in each of the remaining 170 patients. The patients were subdivided into 3 groups based on the duration and heart rate of the ventricular arrhythmia. bpm indicates beats per minute.

**Table 1. Patient Characteristics at Baseline**

	Control, n=37	Overall VA, n=170	nsVA, n=32	nsVT, n=134	VT, n=4
Age, y	60±12	63±11	66±13	63±11	59±12
Sex (male)	28 (76)	147 (87)	30 (94)	116 (87)	1 (100)
Leading cardiac disease					
I-CMP	26 (70)	96 (57)	21 (66)	74 (56)	1 (33)
NI-CMP	11 (30)	72 (43)	11 (34)	59 (43)	2 (67)
LVEF (%)	29±5	27±6	28±6	27±6	29±4
Smoking	21 (57)	110 (66)	18 (56)	91 (68)	1 (33)
Diabetes mellitus	9 (24)	46 (27)	7 (22)	37 (28)	2 (67)
Hypertension	19 (51)	99 (59)	23 (72)	74 (56)	2 (67)
β-blocker	37 (100)	156 (93)	30 (94)	125 (94)	1 (33)
ACEi/ARB	26 (70)	129 (77)	21 (66)	105 (79)	3 (100)
MRA	28 (76)	132 (79)	26 (81)	104 (78)	2 (67)
Statin	26 (70)	115 (69)	22 (69)	91 (68)	2 (67)
Class I or III antiarrhythmic drugs	1 (3)	1 (0.6)	0 (0)	1 (0.6)	0 (0)

Data are expressed as mean±SD or as number (percentage). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; I-CMP, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NI-CMP, nonischemic cardiomyopathy; nsVA, nonsustained ventricular arrhythmia; nsVT, nonsustained ventricular tachycardia; VA, ventricular arrhythmia; and VT, sustained ventricular tachycardia.

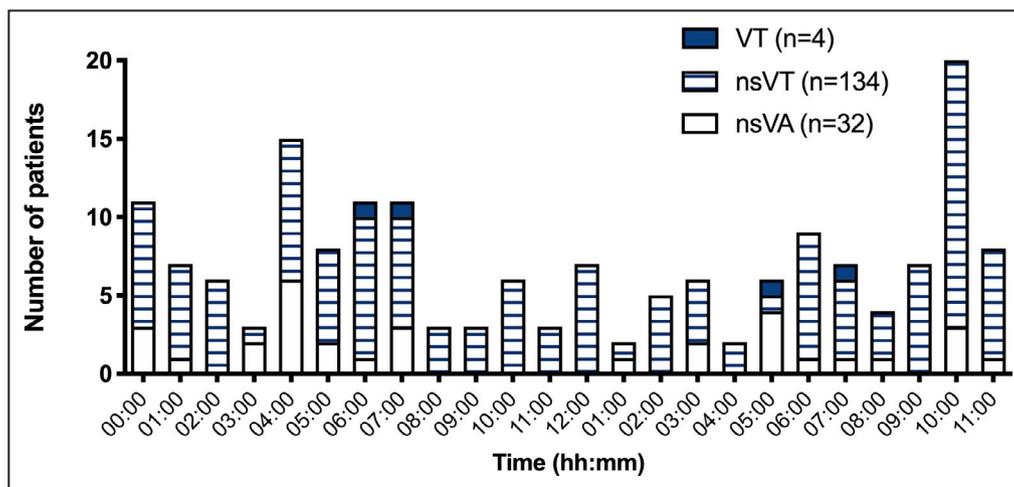
No statistically significant differences were found. Missing values for sex: 3 in the VT group; for other characteristics: 1 in the nsVT group and 1 in the VT group.

day with a peak at 10:00 PM. The VTs occurred in the morning between 6:00 and 7:00 AM, and in the early evening between 5:00 and 7:00 PM. The mean heart rate of all ventricular arrhythmias was 127±30 bpm, 82±12 bpm during nsVA, 136±22 bpm during nsVT, and 177±26 during VT. The duration of ventricular arrhythmias overall was 5±6 seconds, nsVA lasted for 5±4 seconds, nsVT lasted for 4±3 seconds, and VT lasted for 39±2 seconds. The number of complexes during the ventricular arrhythmia was 12±18 in general, nsVA lasted for 8±5 complexes, nsVT

lasted for 10±6 complexes, and VT lasted for 116±12 complexes.

### Electrophysiological Parameters

Table 2 summarizes the electrophysiological parameters at baseline and before the ventricular arrhythmia. At baseline, no significant differences were observed between the groups for the RR, QT, and QTc intervals and STV<sub>QT</sub>. Overall, the heart rate before the ventricular arrhythmias was significantly higher than the heart rate



**Figure 3. Diurnal distribution of ventricular arrhythmia occurrence.**

The number of patients exhibiting their longest ventricular arrhythmia during 1 day. Four patients had VT, which were clustered in the morning (6:00–7:00 AM) and early evening (5:00–7:00 PM). nsVA indicates nonsustained ventricular arrhythmia; nsVT, nonsustained ventricular tachycardia; and VT, sustained ventricular tachycardia.

**Table 2. Electrophysiological Parameters**

	Control, n=37	Overall VA, n=170	nsVA, n=32	nsVT, n=134	VT, n=4
Baseline					
RR interval	1013±129	979±166	1009±155	972±170	972.0±128.6
QT interval	441±45	427±44	426±42	427±44	412±32
QTc interval	439±39	446±46	424±32	432±34	414±39
STV <sub>QT</sub>	0.75±0.23	0.84±0.47	0.80±0.43	0.90±0.49	1.05±0.22
Before VA (last 31 complexes)					
RR interval	967±141	929±152*	1008±132	914±150*,‡	769±137*,‡
QT interval	429±51	412±49*	427±40	409±51*	384±36*
QTc interval	434±42	429±43*	425±30	422±44*	415±16
STV <sub>QT</sub>	0.82±0.26	1.18±0.74*,†	1.18±0.78*,†	1.14±0.70*,†	2.33±1.25*,†

Data are expressed as mean±SD in milliseconds. nsVA indicates nonsustained ventricular arrhythmia; nsVT, nonsustained ventricular tachycardia; STV<sub>QT</sub>, short-term variability of the QT interval; VA, ventricular arrhythmia; and VT, sustained ventricular tachycardia.

\**P*<0.05 compared with baseline within the group.

†*P*<0.05 compared with control group.

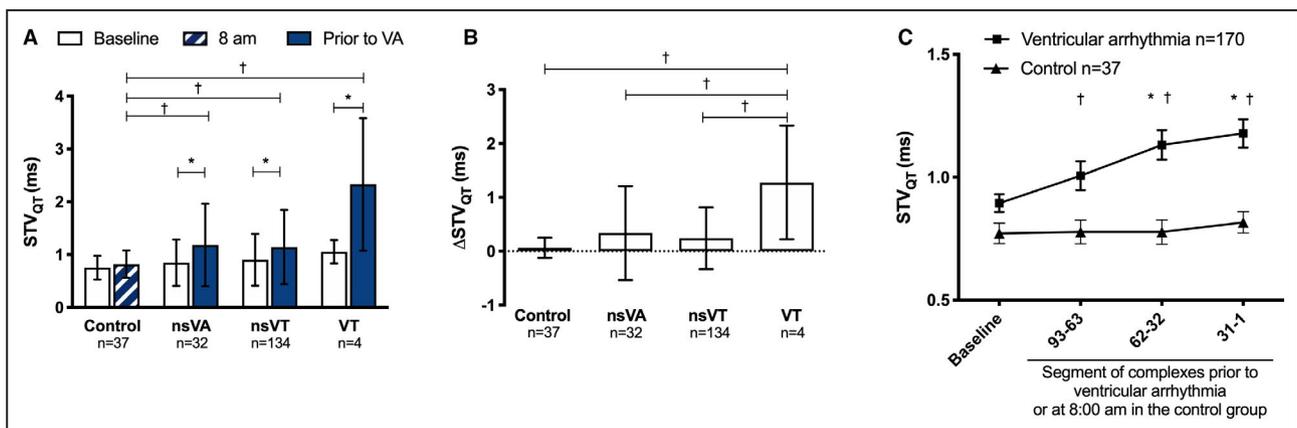
‡*P*<0.05 compared with nsVA.

in baseline, with the exception of patients exhibiting nsVA. The QT and QTc intervals were shorter before nsVT and VT compared with baseline, but were the same before nsVA and their respective baseline values. In the control group there were no differences in the RR, QT, and QTc intervals between 3:00 AM and 8:00 AM.

### STV<sub>QT</sub> Increases Before Ventricular Arrhythmias

The behavior of STV<sub>QT</sub> before a ventricular arrhythmia compared with baseline is shown in Figure 4. STV<sub>QT</sub> did not change in the control group between 3:00 AM and 8:00 AM, from 0.75±0.23 ms to 0.82±0.26 ms, respectively. STV<sub>QT</sub> increased significantly before

nsVA and nsVT, from 0.80±0.43 ms at baseline to 1.18±0.78 ms in the last 31 complexes before nsVA and from 0.90±0.49 ms at baseline to 1.14±0.70 ms in the last 31 complexes before nsVT. The increase in STV<sub>QT</sub> was most pronounced in patients with VT, from 1.05±0.22 ms at baseline to 2.32±1.25 ms in the last 31 complexes before VT. This observation was confirmed by comparing the  $\Delta$ STV<sub>QT</sub> between the groups, whereby  $\Delta$ STV<sub>QT</sub> was significantly higher in VT compared with nsVT (+1.28±1.05 ms versus +0.24±0.57 ms), compared with nsVA (+0.34±0.87 ms), and compared with the control group (+0.07±0.18 ms). The STV<sub>QT</sub> increased progressively during the segments preceding the ventricular arrhythmia, as portrayed in Figure 4c. Compared with baseline, STV<sub>QT</sub> was increased in the segment of 62 to 32 beats onward before ventricular



**Figure 4. Behavior of STV<sub>QT</sub> before ventricular arrhythmia.**

**A**, STV<sub>QT</sub> of the last 31 complexes increases before a ventricular arrhythmia. Data are expressed as mean±SD. **B**,  $\Delta$ STV<sub>QT</sub> is higher before VT than nsVA and nsVT. Data are expressed as mean±SD. **C**, STV<sub>QT</sub> is increased from the segment 62 to 32 complexes before a ventricular arrhythmia and onward. Data are expressed as mean±SEM. \**P*<0.05 within-group comparison; †*P*<0.05 between-group comparison.  $\Delta$ STV<sub>QT</sub> indicates STV<sub>QT</sub> before ventricular arrhythmia minus STV<sub>QT</sub> at baseline; nsVA, nonsustained ventricular arrhythmia; nsVT, nonsustained ventricular tachycardia; STV<sub>QT</sub>, short-term variability of the QT interval; and VT, sustained ventricular tachycardia.

arrhythmia. This translates to approximately 60 to 30 seconds before the ventricular arrhythmia based on the mean heart rate of 65 bpm (RR interval of  $929 \pm 152$ ; Table 2).  $STV_{QT}$  was stable in the segments around 8:00 AM in the control group and continuously lower than the overall group with ventricular arrhythmias.

## DISCUSSION

The results of the current study in patients with primary prophylactic ICD can be summarized as follows: (1) temporal dispersion of repolarization quantified as  $STV_{QT}$  increases before ventricular arrhythmias compared with baseline conditions; (2) in the absence of ventricular arrhythmias,  $STV_{QT}$  remains stable between baseline conditions at 3:00 AM and at 8:00 AM; (3) the increase in  $STV_{QT}$  progresses during the minutes preceding a ventricular arrhythmia and is significantly higher from the segment of 62 to 32 beats before the ventricular arrhythmia and onward; and (4)  $STV_{QT}$  increases more before VT compared with nsVA and nsVT, when it is expressed as  $\Delta STV_{QT}$ .

### Increase in Temporal Dispersion of Repolarization Reflects a Compromised Repolarization Reserve

To our knowledge, this is the first study showing that an increased temporal dispersion of repolarization, quantified as  $STV_{QT}$ , precedes the imminent occurrence of ventricular arrhythmias in patients with primary prophylactic ICD. In animal models, the importance of temporal dispersion of repolarization in arrhythmogenesis has been studied extensively.<sup>6,12,19</sup> Ventricular remodeling attributed to volume overload in the canine model of complete chronic atrioventricular block includes electrical (downregulation of the slowly ( $I_{Ks}$ ) and rapidly ( $I_{Kr}$ ) activating delayed rectifier potassium channels),<sup>20</sup> contractile (altered calcium handling),<sup>21–24</sup> and structural remodeling.<sup>25</sup> Electrical remodeling results in a diminished repolarization reserve, which renders the heart unable to withstand stressors on repolarization.<sup>25</sup> This repolarization lability manifests itself as a prolongation of repolarization duration and an increased temporal dispersion of repolarization.<sup>6,12</sup> When repolarization is challenged further by, for example, an  $I_{Kr}$ -blocking drug, this can act as a final hit on the repolarization reserve.<sup>26</sup> In combination with the altered calcium handling this gives rise to early afterdepolarizations *in vitro*<sup>12,21</sup> and ventricular ectopy and Torsade de Pointes arrhythmias *in vivo*.<sup>12,27</sup> These arrhythmias are preceded by an increase in STV, whereas STV remains low in nonsusceptible subjects.<sup>12,13</sup> Moreover, the severity of the arrhythmic outcome in the chronic atrioventricular block dog is also correlated to the  $\Delta STV$ , as in this patient population.<sup>28</sup> The current study suggests

that a reduced repolarization reserve and triggered activity play a role in arrhythmogenesis in a broad patient population with both ischemic and nonischemic cardiomyopathy.

### Proarrhythmic Component of $STV_{QT}$ That Is Independent of the QT-Interval Duration

Although  $STV_{QT}$  is based on QT-interval measurements, these parameters show a different circadian rhythm and behave differently before ventricular arrhythmias. The circadian rhythm of the QT interval has a cosine curve with a longer QT interval at night around 3 AM and a shorter QT interval in the afternoon around 2:00 PM.<sup>29</sup> This has been attributed to diurnal changes in potassium ion channel function.<sup>30</sup> Similarly, the QT interval of our current study was the longest at baseline, between 1:30 and 4:30 AM.  $STV_{QT}$  also exhibits a circadian pattern in patients with a higher burden of ventricular ectopy and nsVT, whereby there is a peak in  $STV_{QT}$  at 8:00 AM and 6:00 PM.<sup>17</sup> These peaks coincide with the circadian distribution of SCD<sup>31</sup> and are consistent with the occurrence of VT in our study population. It has been hypothesized that the circadian pattern of  $STV_{QT}$  relies on the autonomic nervous system.<sup>17,32</sup> Interestingly, both peaks of  $STV_{QT}$  coincide with the maximum slope in the diurnal cosine curve of the QT interval, suggesting that these are 2 different, yet potentially related, parameters.

Moreover, our finding that  $STV_{QT}$  increases before ventricular arrhythmias without prolongation of the QT interval contributes to the hypothesis that there is an independent proarrhythmic component responsible for an increase in  $STV_{QT}$ . The QT interval is a well-known and broadly applied electrophysiological parameter for proarrhythmic assessment. However, preclinical studies in different animal models indicate that STV is superior to the repolarization duration in predicting the development of imminent ventricular arrhythmias and assessing the efficacy of antiarrhythmic interventions.<sup>19,33</sup> In the chronic atrioventricular block dog model, repolarization duration prolonged upon a challenge of the repolarization irrespective of the arrhythmic outcome, whereas STV only increased in subjects that were susceptible for ventricular arrhythmias.<sup>6,12</sup>

### Clinical Implications

Preclinical studies have demonstrated that STV can be used to monitor the risk for imminent ventricular arrhythmias and initiate a preventive treatment.<sup>14,34</sup> This study shows that STV has a similar behavior before ventricular arrhythmias in patients with a primary prophylactic indication for ICD therapy. Currently, patients at risk for ventricular arrhythmias and SCD are implanted with an ICD. Although the ICD can successfully terminate ventricular arrhythmias with anti-tachy

pacing or a defibrillation shock, the ICD is not able yet to prevent the arrhythmias from occurring. The detrimental effects of ventricular arrhythmias and the reduced quality of life as a result of anxiety for shock therapy give cause to seek further improvement of the ICD.<sup>35</sup> STV can be derived reliably from electrogram signals that are continuously recorded by the ICD.<sup>13</sup> Therefore, the ICD could be used for continuous monitoring of arrhythmic risk by measuring STV on intracardiac signals. A preventive therapy has also been explored in the chronic atrioventricular block dog model in the form of temporary accelerated pacing, where the pacing rate was gradually increased from 60 to 100 bpm in 20 seconds, and successfully prevented an electrical storm from occurring in 70% of the cases.<sup>14</sup> Our study shows that the increase in STV<sub>QT</sub> in patients is present in the segment 60 to 30 seconds before the ventricular arrhythmia, which provides sufficient time to initiate the preventive therapy. To implement this methodology, STV should be determined automatically by the device and the pacing regimen initiated once a certain threshold of STV is reached.

### Strengths and Limitations

STV determination requires accurate measurement of the QT interval because of the unit of the variation. This requirement was addressed in two ways. First, the 24-hour ECG Holter recordings had a high resolution of 1 kHz. Second, measurement of the QT interval was done with a validated semiautomated program to minimize errors in measurement.<sup>17</sup>

The present study also has limitations. The number of patients with a VT is limited because ECG Holter recordings were recorded for only 24 hours in patients without a history of VT. The results in the VT group should therefore be interpreted with caution. More patients with VT can be studied when STV is monitored continuously with an implanted device for a longer period of time. It is also evident that STV cannot be measured reliably in patients with an irregular heart rate attributed to, for example, atrial fibrillation. Furthermore, STV measurements are influenced by the quality of the signals; therefore, many patients were excluded because of noise. When the intracardiac electrogram can be used for STV analysis, reasons for exclusion in the current study, such as noise and a flat T-wave, would be minor issues, and approximately three quarters of the patients would be eligible for STV analysis.

### CONCLUSIONS

This is the first clinical work to demonstrate that STV<sub>QT</sub> increases before imminent ventricular arrhythmias in patients with a primary prophylactic ICD indication and

that the extent of the increase is associated with the severity of the ventricular arrhythmia. These data set a precedent that STV<sub>QT</sub> can be used for imminent ventricular arrhythmia risk monitoring.

### ARTICLE INFORMATION

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#### Disclosures

None.

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