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ORIGINAL RESEARCH

# Temporal Changes in Beat-to-Beat Variability of Repolarization Predict Imminent Nonsustained Ventricular Tachycardia in Patients With Ischemic and Nonischemic Dilated Cardiomyopathy

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**BACKGROUND:** An increase in beat-to-beat variability of repolarization (BVR) predicts arrhythmia onset in experimental models, but its clinical translation is not well established. We investigated the temporal changes in BVR before nonsustained ventricular tachycardia (nsVT) in patients with implantable cardioverter defibrillator (ICD).

**METHODS AND RESULTS:** Patients with nsVT on 24-hour Holter before ICD implantation for ischemic cardiomyopathy (ischemic cardiomyopathy+nsVT, n=43) or dilated cardiomyopathy (dilated cardiomyopathy+nsVT, n=37), matched ICD candidates without nsVT (ischemic cardiomyopathy-nsVT, n=29 and dilated cardiomyopathy-nsVT, n=26), and patients without ICD without structural heart disease (n=50) were studied. Digital Holter recordings from these patients were analyzed using a modified fiducial segment averaging technique to detect the QT interval. The nsVT episodes were semi-automatically identified and QT-BVR was assessed 1-, 5-, and 30-minutes before nsVT, and at rest (at 3:00 AM). Resting BVR was higher in ICD patients compared with controls without structural heart disease. In ICD patients with nsVT, BVR increased significantly 1-minute pre-nsVT in ischemic cardiomyopathy (2.21±0.59 ms, versus 5 minutes pre-nsVT: 1.78±0.50 ms, $P<0.001$) and dilated cardiomyopathy (2.09±0.57 ms, versus 5-minutes pre-nsVT: 1.58±0.51 ms, $P<0.001$), but not in patients without nsVT. In multivariable Cox regression analysis, pre-nsVT BVR was a significant predictor for appropriate therapy during follow-up.

**CONCLUSIONS:** Baseline BVR is elevated and temporal changes in BVR predict imminent nsVT events in patients with ICD independent of underlying cause. Real-time BVR monitoring could be used to predict impending ventricular arrhythmia and allow preventive therapy to be incorporated into ICDs.

**Key Words:** arrhythmia prediction ■ beat-to-beat variability of repolarization ■ Holter ■ nonsustained ventricular tachycardia

Sudden cardiac death (SCD) by sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) remains a major mode of death. Patients with advanced heart disease or cardiomyopathy are at a high risk of SCD.[1] Implantable cardioverter defibrillators (ICD) are currently the most effective intervention to prevent SCD in these high-risk patients.[2] ICDs continuously monitor the cardiac rhythm, detect sustained VT or VF rapidly, and provide antitachycardia pacing or shocks to restore sinus rhythm upon detection.

Identification of patients at increased risk remains challenging because current guidelines utilize clinical

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## Clinical Perspective

### What Is New?

- Beat-to-beat variability of repolarization increase predicts imminent arrhythmias in experimental models; its usefulness in clinical practice of impending arrhythmia risk prediction needs to be established.
- Beat-to-beat variability of repolarization is increased in patients with structural heart disease selected for implantable cardioverter defibrillator implantation compared with patients without structural heart disease.
- Beat-to-beat variability of repolarization reproducibly increases in the minute preceding nonsustained ventricular tachycardia in implantable cardioverter defibrillator candidates regardless of underlying cardiomyopathy (ischemic and nonischemic).

### What Are the Clinical Implications?

- The magnitude of beat-to-beat variability of repolarization in the minute preceding arrhythmia is a predictor of future appropriate implantable cardioverter defibrillator shocks as a surrogate for sudden cardiac death risk.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **APT** | appropriate ICD therapy |
| **BVR** | beat-to-beat variability of repolarization |
| **DCM** | dilated cardiomyopathy |
| **ICM** | ischemic cardiomyopathy |
| **nsVT** | nonsustained ventricular tachycardia |
| **SCD** | sudden cardiac death |
| **SHD** | structural heart disease |

assessment with left ventricular ejection fraction as a main factor to identify high-risk patients.[3] However, several other parameters have been shown to be powerful tools in risk stratification. Further risk assessment using noninvasive tools and parameters including cardiac imaging (for underlying pathology including fibrosis and infarction), ECG analysis (for conduction abnormalities, fragmentation, and repolarization abnormalities, among other risk markers) and 24-hour Holter monitoring (to capture rare events such as nonsustained VT [nsVT] or VT/VF) can be used to improve stratification.[4]

In high-risk patients, prediction of imminent arrhythmia could have a cardinal role in the management of patients with ICDs by triggering preventive device therapy.[5] Device algorithms incorporating known risk factors for SCD are being implemented in early warning systems that can preventatively manage arrhythmias by monitoring and analyzing cardiac electrical activity.[6] Electrical instability is a hallmark of the substrate that sustains arrhythmia. Thus, measures of labile or heterogeneous repolarization have been proposed for identification of short-term arrhythmia vulnerability.[4]

Beat-to-beat variability of repolarization (BVR) or short-term variability is a measure of temporal dispersion that first showed excellent predictive value in predicting drug-induced torsades de pointes in experiments using a dog model of chronic atrioventricular block and cardiac hypertrophy.[7] BVR also has been shown to be elevated in patients with cardiomyopathy, suggesting its usefulness in identifying long-term high-risk patients.[8] However, evidence supporting its usefulness in predicting imminent events in the clinical setting remains limited and it is unclear whether this depends on the cause of the underlying cardiomyopathy.[9]

In this study, we compare the behavior of BVR in patients with an underlying ischemic or nonischemic cardiomyopathy with and without nsVT and a matched control group of patients without overt cardiovascular disease. We also assess the clinical value of BVR in predicting appropriate ICD therapy (APT) during follow-up in our cohort.

# METHODS

The data presented in this article are available from the corresponding author upon reasonable request.

## Patient Population and Study Design

This retrospective study, in accordance with the Declaration of Helsinki, was approved by the ethical committee of the University Hospitals of Leuven (S56074). In view of the retrospective nature of the study, the ethical committee waived the necessity of informed consent. All patients who had a first ICD implanted at the University Hospitals of Leuven are included in an electronic registry as described previously.[10] All patients in this registry from January 1, 2008 until December 31, 2018, who had a minimum follow-up of 1 year were considered for this study. Patients with ischemic (ICM) or dilated nonischemic (DCM) cardiomyopathy and indication for an ICD in primary or secondary prevention of SCD under current guidelines were screened for inclusion.[11] Only ICD candidates with a preprocedural Holter monitor that was digitally available were further considered in the study. ICD candidates who experienced an episode of nsVT (defined as 3 or more consecutive ventricular complexes >100 beats per minute [bpm]) during the 24-hour Holter monitoring were included as cases divided into 2 groups according to their underlying cardiomyopathy: ICM+nsVT group 1 and DCM+nsVT group 2

(Figure 1). ICD candidates without nsVT were matched by age and sex into 2 control groups: ICM-nsVT group 3 and DCM-nsVT group 4 (Figure 1).

A control group of patients with cryptogenic stroke, in whom no obvious structural heart disease (SHD) was present based on medical history, ECG, echocardiography, 24-hour Holter monitoring, and duplex ultrasound of the carotid arteries (meeting the criteria for embolic stroke of unknown source) in the period between 2008 and 2018 were screened. From this group with embolic stroke of unknown source, 50 patients, matched individually by age and sex to 50 randomly selected ICD candidates (from the 80 patients with ICD with nsVT [28 ICM+nsVT and 22 DCM+nsVT]), were studied (Figure S1). Given that acute stroke may alter cardiac repolarization,[12] the electrocardiographic and Holter assessments were conducted after the period of the acute stroke was resolved. For all patients, baseline demographic data including age, sex, and body mass index; clinical data including medical history, medications, left ventricular ejection fraction and serum creatinine; as well as electrophysiological parameters from baseline 12-lead ECG were collected from hospital records (Table 1 and Table S1). The baseline ECG QT interval was corrected using the Fridericia or Rautaharju formula for narrow and broad QRS complexes, respectively.[13]

A 2-part study with a case–control followed by cohort study design was used. In the first part, we performed a case–control study investigating the predictive value of repolarization lability (BVR) in the minutes preceding nsVT. The ICD candidates with nsVT (ICM+nsVT and DCM+nsVT) were cases while patients without nsVT (ICM-nsVT and DCM-nsVT) were controls. In the second part of the study, the cohort of ICD patients with nsVT (ICM+nsVT and DCM+nsVT) on pre-implantation Holter monitor were investigated for factors predicting APT during follow-up in patients with nsVT.

## Holter Analysis

Twenty-four-hour ambulatory 2- or 3-channel Holter ECG recordings were performed using standard 200-Hz Spiderview recorders (Microport, France). Holter recordings of all patients included in the study were processed and exported as ISHNE-files using Synescope Holter software (Microport, France). Holter processing utilized a template-based algorithm to analyze the 24-hour Holter for baseline electrophysiological parameters including the duration of time analyzed of the total recorded time as a quality parameter, average heart rate, number of bradycardia episodes defined as heart rate <50 bpm, number of pauses >2000 ms, number of atrial- and ventricular extrasystoles as well as nonsustained (<30 seconds) and sustained VT episodes. The Holter recordings were semi-automatically analyzed and manually corrected where necessary.

The ISHNE files were then imported and analyzed using R-DECO, a custom-made signal analysis software developed in MATLAB (Mathworks, Natick, MA, USA).[14] The Holter recordings were filtered using a backward/forward high-pass second-order Butterworth filter to exclude low-frequency variation (specifically respiration motion with a cut-off frequency of 0.5 Hz, and a notch filter at 50 Hz to suppress electrical interference and high-frequency noise). Then, a modified fiducial segment averaging technique was used to analyze the QT duration of complexes in the segment as described previously.[14] Briefly, the QRS complex of each beat was detected using an envelope-based algorithm combined with an adaptive

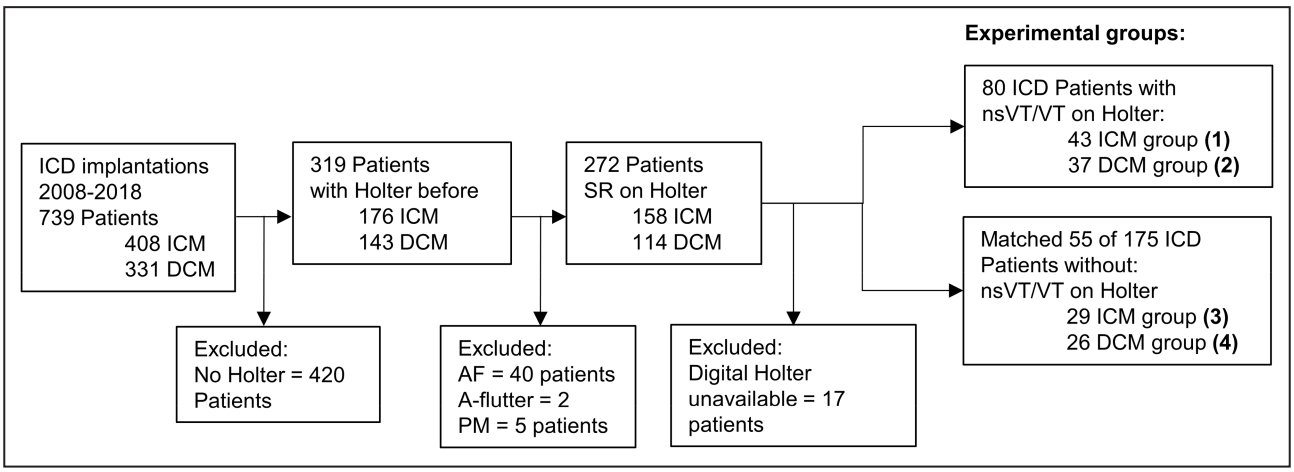


**Figure 1. Experimental design.**
Study flow chart illustrating patient inclusion and study groups. Patients with ischemic heart disease (IHD) and dilated cardiomyopathy (DCM) admitted for implantable cardiac defibrillator (ICD) implantation were considered. All patients without a prior Holter recording or where the Holter was unavailable, and patients with atrial fibrillation (AF) or permanent pacing (PM) were excluded. AF indicates atrial fibrillation; A-flutter, atrial flutter; ICM, ischemic cardiomyopathy; nsVT, nonsustained ventricular tachycardia; PM, pacemaker device; SHD, structural heart disease; SR, sinus rhythm; and VT, ventricular tachycardia.

**Table 1. Patient Baseline Characteristics**

| | ICD candidates with nsVT | | ICD candidates without nsVT | |
|---|---|---|---|---|
| | ICM | DCM | ICM | DCM |
| n | 43 | 37 | 29 | 26 |
| Age, y | 66 (57–70) | 57 (44–67)* | 66 (58–70) | 59 (46–67)‡ |
| Sex | | | | |
| Male (%) | 39 (90.6) | 26 (70.3)* | 26 (89.6) | 18 (69.2) |
| Female (%) | 4 (9.3) | 11 (29.7)* | 3 (10.3) | 8 (30.8) |
| BMI | 27±4.0 | 25.4±4.6 | 25±4.6 | 26.7±5.0 |
| NYHA (%) | | | | |
| 1 | 15 (34.9) | 8 (21.6) | 9 (31.0) | 6 (23.1) |
| 2 | 16 (34.9) | 19 (51.4) | 11 (37.9) | 11 (42.3) |
| 3 | 12 (27.9) | 10 (27.0) | 9 (31.0) | 9 (34.6) |
| 4 | 1 (2.3) | 0 (0) | 0 (0.0) | 0 (0.0) |
| LVEF, % | 28.6±8.8 | 27.3±10.5 | 28.1±9.2 | 29.7±11.5 |
| Indication (%) | | | | |
| Primary | 36 (83.7) | 35 (94.6) | 22 (78.5) | 24 (88.9) |
| Secondary | 7 (16.2) | 2 (5.4) | 6 (21.4) | 3 (11.1) |
| History (%) | | | | |
| Stroke/TIA | 6 (14.0) | 4 (10.8) | 5 (17.2) | 2 (7.7) |
| Diabetes | 19 (44.1) | 9 (24.3)* | 5 (17.2)* | 4 (15.4) |
| AF | 5 (11.6) | 2 (5.4) | 8 (27.6) | 5 (19.2) |
| Hypertension | 29 (67.4) | 8 (21.6)† | 20 (69.0) | 9 (34.6)§ |
| Creatinine, mg/dL | 1.10±0.39 | 1.10±0.31 | 1.24±0.38 | 1.21±0.48 |
| Medications (%) | | | | |
| β-Blocker | 40 (93.0) | 33 (89.2) | 26 (89.7) | 24 (92.3) |
| Statin | 42 (97.7) | 16 (43.2) | 25 (86.2) | 20 (76.9) |
| ACE-I/ARB | 42 (97.7) | 31 (83.2) | 26 (89.7) | 24 (92.3) |
| Loop diuretic | 14 (32.0) | 22 (59.4) | 18 (62.1) | 11 (42.3) |
| MRA | 27 (62.2) | 28 (75.7) | 16 (55.2) | 15 (57.7) |
| Aspirin | 34 (79.9) | 12 (32.4)† | 22 (75.9) | 18 (69.2)§ |
| VKA | 11 (25.5) | 7 (18.1) | 10 (34.5) | 6 (23.1) |
| NOAC | 0 (0) | 1 (2.0) | 2 (6.9) | 0 (0) |
| Amiodarone | 7 (16.6) | 4 (10.7) | 3 (10.3) | 1 (3.8) |
| Other AAD | 1 (2.3) | 2 (5.4) | 2 (6.9) | 2 (7.7) |
| ECG | | | | |
| Heart rate, bpm | 67.7±12.6 | 66.4±14.9 | 63.6±13.4 | 67.7±12.6 |
| QRS, ms | 123.5±28.2 | 119.8±29.9 | 130.3±35.4 | 126.0±26.7 |
| QT, ms | 424 (412–444) | 422 (397–449) | 434 (418–486) | 426 (408–445) |
| QTc, ms | 448±41.8 | 439±37.1 | 432±42.9 | 443±33.9 |
| LBBB (%) | 11 (25.6) | 11 (29.7) | 5 (17.2) | 8 (30.7) |
| RBBB (%) | 4 (9.3) | 1 (2.7) | 2 (6.9) | 1 (3.8) |

Data expressed as n (%) and mean±SD or median (interquartile range). 2-way ANOVA or Fisher exact with Bonferroni post hoc analysis. AAD indicates anti-arrhythmia drug; ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; BMI, body mass index; bpm, beats/minute; DCM, dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NOAC, novel oral anticoagulant; nsVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association classification of heart failure; QTc, QT corrected by (Fridericia or Rautaharju formula for narrow and broad QRS complexes, respectively);[13] RBBB, right bundle branch block; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

*$P$<0.05, †$P$<0.001, vs ICM+nsVT; ‡$P$<0.05 and §$P$<0.01, vs ICM-nsVT.

thresholding. Correct detection and annotation of the QRS complexes was manually checked and corrected where necessary. All ventricular premature complexes as well as the preceding (if the premature complex occurred before the end of the T-wave) and the succeeding sinus beats were excluded from the analysis.

The annotated sinus QRS complexes were aligned by the dominant R/Q wave and used to create template complexes. The onset of the Q-wave and end of the T-wave were detected by modified compression and integration algorithms based on the template complex as previously described.[15] Annotations were used to determine the QT duration of each complex. Correct Q-onset and T-end detection were checked and manually adjusted using the tangent method where necessary. Poincaré plots were then constructed from 30 consecutive sinus beats. QT-BVR was calculated using the established formula $\sum|QT_{n+1} - QT_n|/N \times \sqrt{2}$; where N is the number of beats.[7]

In all patients, we defined a 1-minute segment of uninterrupted sinus rhythm at 3:00 AM as baseline. If there were any ventricular extrasystoles at 3:00 AM, a segment an hour later at 4:00 AM was used. This timepoint was selected because it is in the middle of the period when extrasystoles were lowest and least influenced by physical activity and sympathetic nervous signaling during sleep.[16,17] In ICD patients, the first nsVT episode after the 3:00 AM timepoint was semiautomatically detected and annotated. To assess the temporal changes in repolarization lability before the arrhythmic event, 3 timepoints were defined based on the nsVT episode as follows: 1-, 5-, and 30-minutes before the nsVT event. Per definition, control patients did not have nsVT on Holter; therefore, timepoints matched to time of day to respective corresponding ICD patients were selected and BVR was assessed at 1-, 5-, and 30-minutes before this time. At these timepoints, QT-BVR was measured from the lead equivalent to ECG lead II. If this lead was noisy or had a flat T-wave, the alternate lead was used.

In patients who had >1 nsVT episode, a second episode >1 hour following the index was selected to perform the same analysis to assess reproducibility.

## Retrospective Clinical End Points

The primary end point in patients with underlying cardiomyopathy was considered the first APT. APT was defined as either appropriate ICD shock or antitachycardia pacing. The date and precipitating event (VT or VF) of the appropriate ICD shock or antitachycardia pacing was verified from source documents of ICD interrogation by the treating cardiac electrophysiologist. All clinical end points were collected until death, heart transplantation, or the last available outpatient visit before December 31, 2021.

## Statistical Analysis

Data are expressed as mean±SD, median (interquartile range), or number and percentage as appropriate. Two-tailed *t* test, $\chi^2$ test with Fisher exact or 2-way ANOVA with Bonferroni post hoc analysis was used to compare clinical variables between groups. A mixed effects model with Bonferroni post hoc correction was used to compare temporal changes in BVR and between groups. Cox hazard regression analysis was used to compare the contribution of clinical parameters to the end point. Retrospective clinical analysis of appropriate ICD therapy was performed by survival analysis. Kaplan–Meier graphs with log-rank analysis were plotted to assess this end point. Univariate Cox regression analysis was performed for available clinical parameters: underlying cardiomyopathy, age, sex, and left ventricular ejection fraction; electrophysiological parameters: heart rate, QRS duration, and QTc duration; number of nonsustained episodes on Holter; BVR parameters: resting BVR, BVR in the minute preceding nsVT (pre-nsVT BVR), and temporal change in BVR from preceding timepoint. Multivariable Cox regression analysis was performed using a backward elimination strategy including all variables with a $P<0.100$ in univariate analysis. Proportional hazard assumptions were assessed using Schoenfeld residuals and visual interpretation of the proportional hazard plots. Collinearity in the final model was assessed using a covariance matrix of the final model. The Harrell's C-index was calculated for the final model. A $P<0.05$ was considered significant. All statistical analysis was performed using GraphPad Prism v8, SPSS IBM Statistics v27, and Stata v17.

# RESULTS

## Patient Characteristics

The demographic and clinical characteristics of the patients are presented in Table 1. A total of 80 ICD candidates with nsVT, 43 ICM+nsVT, aged 66 (57–70) years and 90.6% male, and 37 DCM+nsVT, aged 57 (44–57) years and 70.3% male; 55 ICD candidates without nsVT, 29 ICM-nsVT, aged 66 (58–70) years and 89% male; and 26 DCM-nsVT, aged 54 (46–67) years and 74% male were studied. Patients with DCM were younger than patients with ICM ($P=0.041$ and $P=0.043$, with and without nsVT, respectively). The patients in all groups were predominantly male, although the ICM+nsVT group had a higher proportion than the DCM+nsVT group ($P=0.024$).

More patients with ICM+nsVT had diabetes (44.1% versus ICM-nsVT: 17.9%, $P=0.037$), and fewer patients with DCM had hypertension (DCM+nsVT 21.6% versus ICM+nsVT: 67.4%, $P<0.001$; DCM-nsVT: 34.6% versus ICM-nsVT: 71.4%, $P=0.015$). Medications were not different between ICM and DCM, with the exception of more aspirin use in patients with DCM+nsVT (DCM+nsVT: 32.4% versus ICM+nsVT: 79.9%, $P<0.001$; DCM+nsVT: 32.4% versus DCM-nsVT: 69.2%, $P=0.005$). There were no differences in ECG parameters between ICM and DCM groups.

## Holter Electrophysiological Parameters

The baseline parameters of the Holter recordings are presented in Table 2 and Table S2. ICD candidates with nsVT had more ventricular extrasystoles per hour than ICD candidates without nsVT (ICM+nsVT: 80.8 [25.0–273.2] versus ICM-nsVT: 3.1 [0.5–10.8], $P<0.001$ and DCM+nsVT: 62.2 [10.3–190.7] versus DCM-nsVT: 7.3 [0.5–29.1], $P<0.001$). In addition, ICM+nsVT had more ventricular extrasystoles than DCM+nsVT ($P=0.004$). There were no other differences in electrophysiological parameters.

The first nsVT episode of the day, used in subsequent analysis, occurred at all hours of the day without distinguishable preferred time-of-day patterns in both groups (Figure 2A). There tended to be more nsVT episodes in ICM+nsVT than DCM+nsVT, but this was not statistically significant (ICM+nsVT: 10.1±6.4 versus DCM+nsVT: 7.9±4.7, $P=0.094$). The number of complexes and rate of the nsVT episodes considered for analysis were comparable ($P=0.676$ and $P=0.582$, Figure 2B).

## Resting BVR in ICD Patients

Figure 3A illustrates the fiducial point detection used to determine the QT interval and an example of the Poincaré plot constructed from 30 consecutive sinus beats to assess the QT-BVR. At baseline, there was no difference in heart rate between the ICD patient groups (ICM+nsVT: 66.9±11.71 ms versus ICM-nsVT 61.2±9.19 ms, $P=0.188$; DCM+nsVT: 63.41±10.95 ms versus DCM-nsVT: 67.29±12.39, $P=0.527$) (Figure 3B). QT-BVR was also not significantly different between the groups (ICM+nsVT: 1.48±0.35 ms versus ICM-nsVT 1.44±0.20 ms, $P=0.957$; DCM+nsVT: 1.43±0.29 ms versus DCM-nsVT: 1.41±0.27, $P=0.983$) (Figure 3B). However, the resting BVR in ICD patients both with ICM and DCM was more than that of the control group of patients without SHD (control: 1.25±0.23 ms versus ICM: 1.46±0.32 ms, $P<0.001$ and DCM: 1.43±0.28 ms, $P=0.003$), although the resting heart rate was not different (Figure S2).

## Temporal Changes in BVR Predict Imminent Ventricular Arrhythmias

Figure 4A illustrates the temporal analysis of QT-BVR before the occurrence of a nsVT event (top insert), or matched timepoints in ICD candidates without nsVT, and examples of the Poincaré plots at 30-, 5-, and 1-minute before the nsVT used for QT-BVR calculation (bottom insert). The timepoints used for analysis in the control groups were matched to nsVT-timepoints of the respective ICD patients in Figure 2A. The time-of-day profile matched timepoints are presented in Figure S3 and reflect the random distribution of nsVT in ICD patients ($P=0.989$).

In ICM ICD candidates with nsVT (ICM+nsVT), the QT-BVR at baseline (1.48±0.35 ms at 3:00 AM) was not different 30 minutes before nsVT (1.41±0.54 ms, $P=0.985$), but thereafter, increased to 1.78±0.50 ms at 5 minutes ($P=0.011$) and further increased to 2.21±0.59 ms at 1 minute before nsVT ($P<0.001$). In contrast, there was no significant change in temporal BVR at matched timepoints in ICM ICD candidates without nsVT (ICM-nsVT) ($P=0.975$, Figure 4B). A

**Table 2. Holter Electrophysiological Parameters**

| | ICD candidates with nsVT | | ICD candidates without nsVT | |
|---|---|---|---|---|
| | ICM | DCM | ICM | DCM |
| No. | 43 | 37 | 29 | 26 |
| Holter quality (hours analyzed) | 22.7±3.5 | 22.5±3.9 | 23.0±0.22 | 23.0±0.26 |
| Heart rate, bpm | 70.9±11.5 | 69.4±12.2 | 66.1±12.7 | 68.3±10.6 |
| Bradycardia episodes | 0 (0–12.8) | 8.5 (0–49.5) | 15 (0–78.8) | 0 (0–23.0) |
| Pauses | 0 (0) | 0 (0) | 0 (0–1) | 0 (0–2) |
| Atrial extrasystoles per h | 3.5 (0.8–13.3) | 1.3 (0.3–8.9) | 1.0 (0.2–5.6) | 0.5 (0.1–5.0) |
| Ventricular extrasystoles per h | 80.8 (25.0–273.2) | 62.2 (10.3–190.7)* | 3.1 (0.5–10.8) | 7.3 (0.5–29.1)† |
| NsVT | | | | |
| Number of episodes | 10.1±6.4 | 7.9±4.7 | 0 | 0 |
| Average rate, bpm | 148.1±30.2 | 150±26.2 | … | … |
| Average duration, s | 2.4 (1.7–3.9) | 2.4 (1.6–3.1) | … | … |
| Sustained VT | | | | |
| Number of patients | 4 | 1 | 0 | 0 |
| Average rate, bpm | 123.5±18.4 | 130.4±0.6 | … | … |

Data expressed as n (%) and mean±SD or median (interquartile range). 1-way ANOVA, Fisher exact with Bonferroni post hoc analysis or 2-tailed *t* test. AV block indicates atrioventricular block episodes; bpm, beats per minute; DCM, dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; nsVT, nonsustained ventricular tachycardia; and VT, ventricular tachycardia.

*$P<0.001$, vs ICM+nsVT; †$P<0.01$, vs DCM+nsVT.

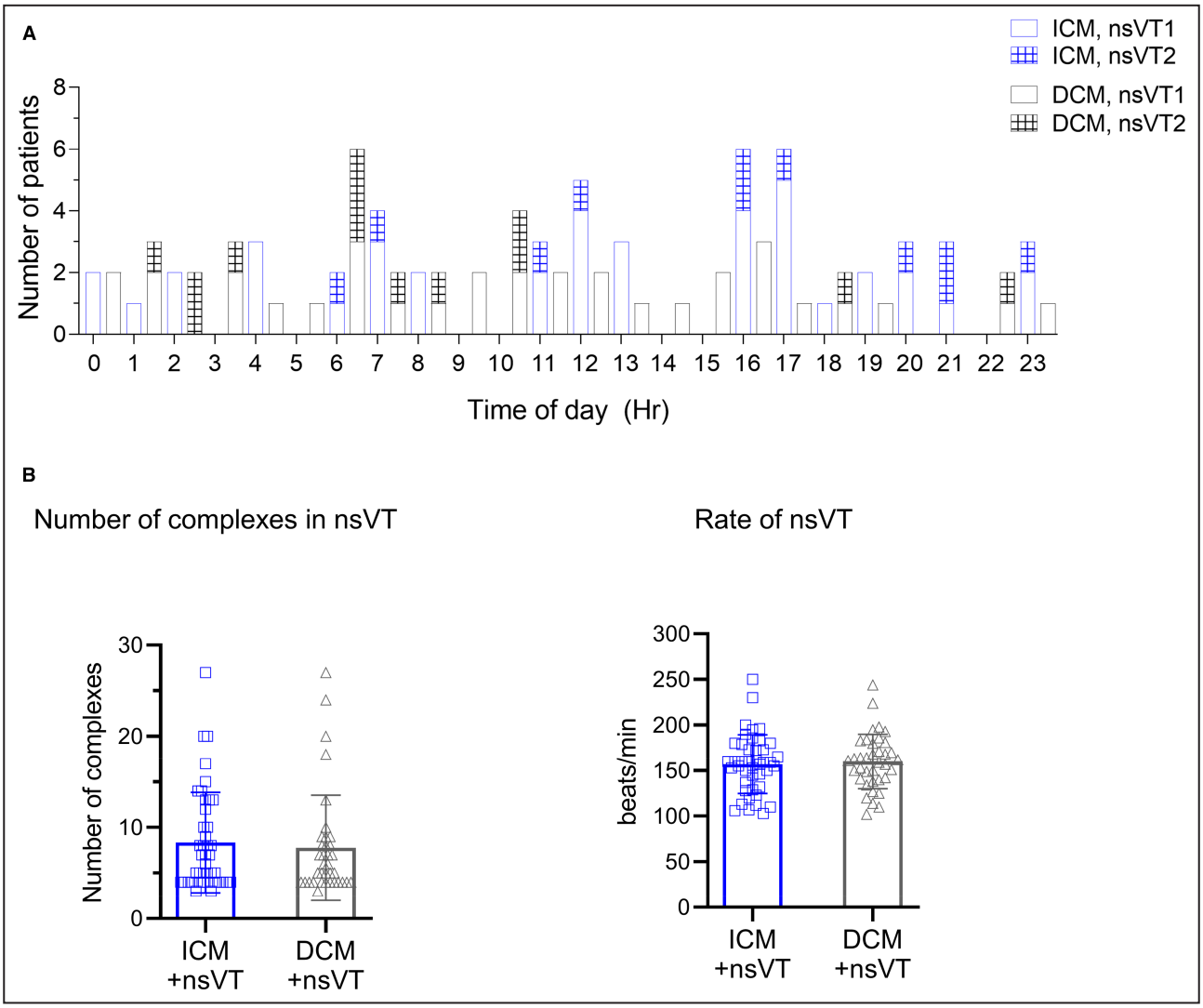


**Figure 2. Characteristics of nonsustained ventricular tachycardia (nsVT) episodes.**
**A**, Time of occurrence during the day of the first and second nsVT episode used for analysis. **B**, Summary data of the number of complexes in the nsVT episodes analyzed (left) and the heart rate during the nsVT episodes (right). N=43 (ICM+nsVT), 37 (DCM+nsVT). 2-tailed *t* test. DCM indicates dilated cardiomyopathy; and ICM, ischemic cardiomyopathy.

similar pattern was seen in the DCM ICD candidates with nsVT (DCM+nsVT), at baseline (3:00 AM); BVR was 1.43±0.29 ms, comparable to 1.38±0.33 ms at 30 minutes before nsVT ($P$=0.757), and tended to increase to 1.58±0.51 ms at 5 minutes ($P$=0.133), then significantly increased to 2.09±0.57 ms at 1 minute before nsVT ($P$<0.001). In DCM ICD candidates without nsVT (DCM-nsVT), no significant BVR differences were observed at matched timepoints ($P$=0.945, Figure 4B). Furthermore, in control patients without SHD, no differences in BVR were observed at matched timepoints ($P$=0.952, Figure S4).

There was no significant difference between the temporal behavior of BVR of the ICM+nsVT compared with DCM+nsVT groups ($P$=0.406), nor was there a significant difference between the change in BVR ($P$=1.000) (Figure 4C). QT-BVR changes in time were similar between ICM+nsVT and DCM+nsVT, but the magnitude of change at 5 minutes to 1 minute before the nsVT was higher in ICM+nsVT than DCM+nsVT (ICM: 0.48±0.54 ms versus DCM: 0.23±0.35, $P$<0.001) (Figure 4C).

These temporal changes in BVR occurred without temporal changes in heart rate in ICM patients with nsVT (3:00 AM: 66.9±11.7 bpm, 30-minutes prematched nsVT time: 70.5±15.0 bpm, 5-minutes prematched nsVT time 68.2±14.5 bpm and 1-minute prematched nsVT time 71.6±16.0 bpm, $P$=1.000) and DCM patients with nsVT (3:00 AM: 63.4±10.9 bpm, 30-minutes prematched nsVT time: 68.8±11.2 bpm, 5-minutes prematched nsVT time 72.2±11.0 bpm and 1-minute prematched nsVT time 69.9±13.1 bpm, $P$=0.985) (Figure S5).

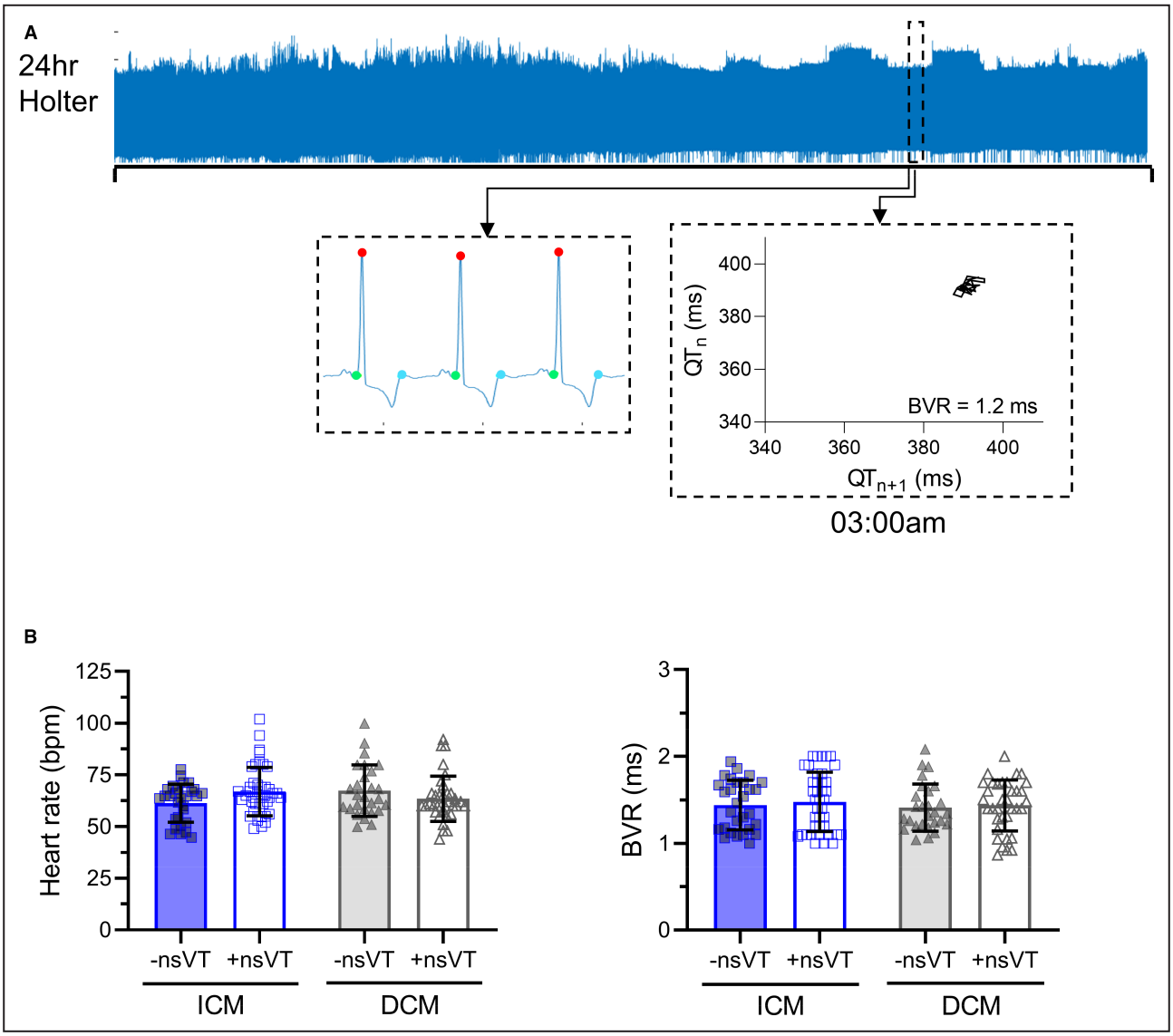


**Figure 3. Beat-to-beat variation of repolarization (BVR) at rest.**
**A**, Example of a condensed 24-hour Holter illustrating the fiducial point QRS, and QT detection and baseline QT-BVR Poincaré plot of a patient with ICM. **B**, Summary data of baseline heart rate (left) and QT-BVR (right) of ICM and DCM patients with and without nsVT, taken at 3:00 AM. N=29 (ICM-nsVT), 43 (ICM+nsVT), 26 (DCM-nsVT), 37 (DCM+nsVT). 2-way ANOVA with Bonferroni post hoc analysis. bpm indicates beats per minute; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; and nsVT, nonsustained ventricular tachycardia.

A total of 17 patients (11 ICM and 6 DCM) had >1 nsVT episode at least 1 hour later. This second event analyzed also occurred at all hours of the day without distinguishable time-of-day patterns in both groups (Figure S6). In these patients, temporal BVR showed a pattern similar to the index event and increased from 1.34±0.60 ms (30 minutes before nsVT) to 1.84±0.76 ms (5 minutes before nsVT) and 2.41±0.79 ms (1 minute before nsVT), $P<0.001$.

## Multivariable Clinical Analysis

The second part of the study considered the predictive value of BVR analyzed on the pre-ICD implantation Holter, for predicting future events and ICD appropriate therapy in patients with preimplantation nsVT. Twenty of the 80 ICD patients with nsVT (25%) received appropriate therapy during follow-up (ICM+nsVT–13 patients [10 VT and 3 VF] and DCM+nsVT–7 patients [7 VT]). There was no difference in event-free survival between ICD and DCM ($P=0.359$, Figure 5). Table 3 presents the regression analysis of clinical and electrophysiological parameters that were assessed as contributors to APT. Univariate analysis identified history of atrial fibrillation, number of nsVT episodes on Holter, and all BVR measurements as significant predictors of appropriate ICD therapy. In multivariable Cox regression analysis, atrial fibrillation and pre-nsVT BVR are independent

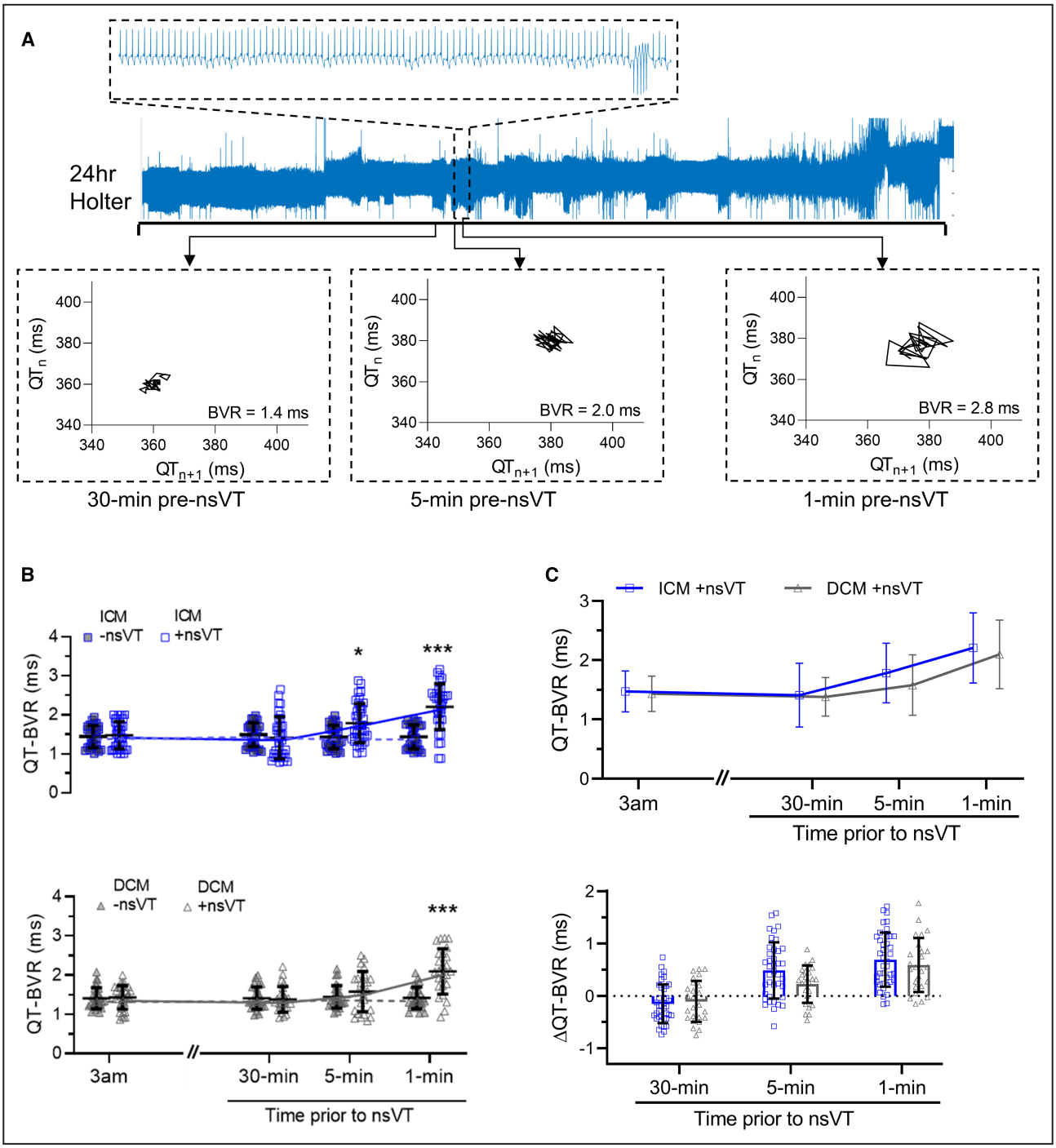


**Figure 4. Temporal changes in beat-to-beat variation of repolarization (BVR) predict nonsustained ventricular tachycardia (nsVT).**

**A**, Example of a condensed 24-hour Holter illustrating the timepoints with pre-nsVT ECG segment, and examples of the QT-BVR Poincaré plots from each segment. **B**, Summary data of temporal changes in QT-BVR in patients with and without nsVT, with ICM (top) and DCM (bottom). N=29 (ICM−nsVT), 43 (ICM+nsVT), 26 (DCM−nsVT), 37 (DCM+nsVT). Mixed effects model analysis with Bonferroni correction. *$P$<0.05, ***$P$<0.001 vs preceding timepoint. **C**, Mean data of the temporal BVR changes in patients with nsVT comparing ICM and DCM patients (top), and summary data of the change in BVR (bottom) between timepoints for patients with nsVT groups, comparing ICM and DCM patients. Mixed effects model analysis with Bonferroni correction. DCM indicates dilated cardiomyopathy; and ICM, ischemic cardiomyopathy.

predictors of appropriate ICD therapy (Harrell's C-index of the final model=0.834).

In this cohort of ICD patients with pre-ICD nsVT, we further compared the clinical variables and BVR in the patients who experienced appropriate therapy to those who did not (Table S3). The number of nsVT episodes, baseline BVR, max BVR, and ΔBVR were higher in patients who received appropriate therapy, with max BVR having the most significant difference (2.59±0.47 ms, versus 1.93±0.54 ms in patients without appropriate therapy, $P<0.001$).

## DISCUSSION

The main findings from this study are as follows: (1) resting BVR is increased in ICD candidates with both underlying ICM and DCM, (2) BVR increases significantly in the minute preceding nsVT events in both ICM and DCM, and (3) BVR is associated with appropriate therapy during follow-up. These findings support the further exploration of BVR in clinical risk stratification and prediction of imminent arrhythmia risk in ICD patients.

### Labile Repolarization in ICD Patients and Arrhythmia Vulnerability

Resting BVR, taken at a timepoint when the patient is assumed to be asleep and physical activity is unlikely, revealed that ICD patients, regardless of underlying cardiomyopathy (ICM and DCM) and presence of nsVT, had higher BVR compared with matched patients without SHD. These findings are consistent with clinical reports of increased BVR in patients with cardiomyopathy[18,19] and heart failure.[8]

The relevance of BVR as a measure of temporal dispersion of repolarization has been demonstrated in various animal models. Increased BVR is present in the remodeled heart of dogs with chronic atrioventricular block susceptible for torsades de pointes,[7] in pigs after myocardial infarction,[20] and in rabbits with long QT syndrome.[21] At a cellular level, BVR is a measure of repolarization reserve and an increased BVR represents a reduced reserve.[22] Thus, increased BVR is a consequence of remodeling of cellular ion channels that contribute to the cellular action potential, particularly repolarizing potassium currents,[23] and calcium handling.[22,24] Such cellular remodeling has been observed in human myocytes isolated from patients with cardiomyopathy and heart failure, which demonstrated reduced repolarizing potassium currents and calcium handling leading to the characteristic prolonged action potential.[25] This may contribute to altered ventricular repolarization and to a prolongation of the QT interval observed in heart failure models[26,27] and patients.[28] This is consistent with our observations of longer QTc in patients with ICM and DCM compared with controls without SHD in the current study.

Our findings support the hypothesis that patients with cardiomyopathy have reduced repolarization reserve, which renders them at increased risk of arrhythmia. They also reinforce the value of assessing repolarization heterogeneity in arrhythmogenesis and its targeting in the prevention of SCD in high-risk patients.

### Usefulness of BVR in Predicting Imminent Arrhythmias

Our data suggest that BVR increases in the minutes preceding nsVT. We observed a similar pattern of BVR increase in patients with ICM and DCM before nsVT but not at matched timepoints in patients with ICM and DCM without nsVT or SHD. At 1 minute before VT, BVR was increased compared with the preceding

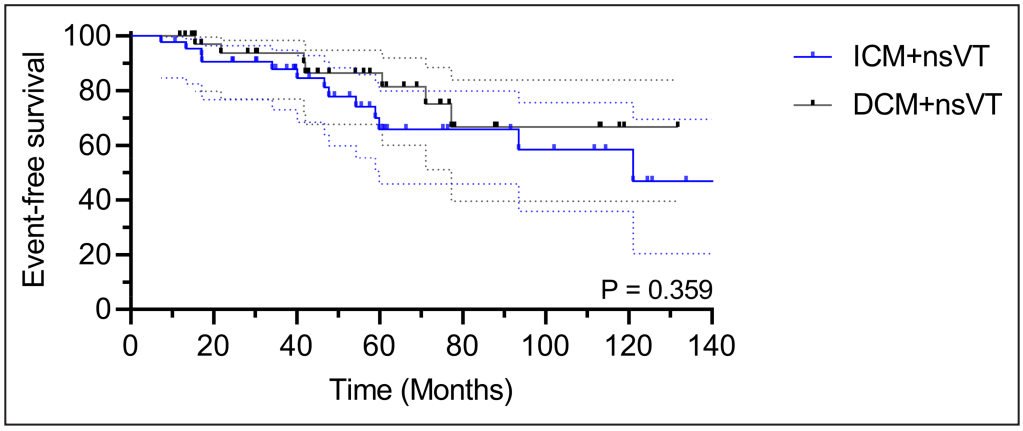


**Figure 5. Kaplan–Meier graphs of freedom from appropriate therapy in ICD patients with nsVT.** N=43 (ICM+nsVT), 37 (DCM+nsVT). Log-rank test. DCM indicates dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; and nsVT, nonsustained ventricular tachycardia.

**Table 3. Cox Regression Analysis for Appropriate ICD Therapy in Patients With Pre-Implantation nsVT on Holter**

| Clinical variable | Univariate regression | | Multivariate regression model | |
|---|---|---|---|---|
| | *P* value | Hazard ratio (95% CI) | *P* value | Hazard ratio (95% CI) |
| N=80 | | | | |
| Male | 0.879 | 1.090 (0.359–3.307) | | |
| Age, /y | 0.161 | 1.029 (0.989–1.071) | | |
| ICM | 0.363 | 1.538 (0.609–3.885) | | |
| LVEF (/%) | 0.225 | 1.025 (0.985–1.066) | | |
| AF | 0.018 | 3.831 (1.254–11.706) | 0.004 | 6.247 (1.809–21.573) |
| ECG | | | | |
| Heart rate, /bpm | 0.288 | 1.019 (0.984–1.055) | | |
| QRS, /ms | 0.829 | 1.002 (0.986–1.018) | | |
| QTc, /ms | 0.094 | 1.009 (0.998–1.020) | | |
| Holter | | | | |
| Ventricular extrasystoles (/unit increase) | 0.647 | 1.000 (1.000–1.000) | | |
| Number of nsVT episodes (/unit increase) | 0.003 | 1.787 (1.212–2.365) | | |
| BVR | | | | |
| Resting, /ms | 0.009 | 5.508 (1.527–19.874) | | |
| Pre-nsVT BVR, /ms | <0.001 | 8.026 (2.855–22.563) | <0.001 | 7.848 (2.638–23.352) |
| Δ BVR, /ms | 0.020 | 2.891 (1.186–7.047) | | |

Variables for the multivariable analysis model were selected by backward elimination model and tested for collinearity. Resting BVR defined as BVR measured at 3:00 AM. AF indicates atrial fibrillation; bpm, beats per minute; BVR, beat-to-beat variability of repolarization; Δ BVR, BVR at 1-minute pre-nsVT minus BVR at 5-minutes pre-nsVT; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; and nsVT, nonsustained ventricular tachycardia.

30-minute timepoint as well as compared with resting BVR in the ICD groups.

BVR has been extensively studied in a dog model of torsades de pointes by the group of M. Vos (Utrecht, The Netherlands), who first demonstrated that this measure of temporal dispersion of repolarization precedes the onset of torsades de pointes.[7] Smoczyńska et al from this group recently demonstrated similar findings in the European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators (EU-CERT) cohort of ICD patients.[9] In this study, of the 2331 EU-CERT patients, 170 primary prophylactic ICD patients with either ICM or DCM and nsVT on 24-hour Holter were included, and 37 randomly selected ICD patients without nsVT were selected as controls. They found that short-term variability or BVR increased by ≈50% in the minute before nsVT. These results are in line with our results, but compared with our analysis Smoczyńska et al did not report possible differences depending on the cause of the underlying cardiomyopathy, and the results were compared only with patients with similar underlying heart disease and not to a control population.

These results, however, are in contrast to those of Sachdev et al,[29] who have not observed repolarization variability in monitoring of acutely ill patients admitted to the Coronary Care Unit who had ventricular arrhythmia during 24-hour ECG monitoring. The confounding effects of sustained autonomic activation in these acutely ill patients, which is in contrast to our cohort of patients with stable cardiomyopathy, likely contribute to the lack of elevated BVR in this study.

## Clinical Implications

In clinical practice, currently no parameters are available that accurately predict the onset of spontaneous arrhythmia. The finding of an increased BVR immediately before ventricular arrhythmia is important because it reinforces its value in prediction of imminent arrhythmia events in high-risk patients and supports its translation to clinical practice, especially for ICD monitoring. Predicting the onset of arrhythmias, particularly in patients with cardiomyopathy, is of clinical importance, because it can open possibilities for preventive strategies to avoid ICD shocks. Sustained arrhythmia and the appropriate ICD shocks are associated with negative cardiac and neurohormonal remodeling that worsen function and may contribute to heart failure.[30] The psychological impact of the arrhythmia-shock sequence of events including anxiety and pain is important to a patient's holistic well-being and, together with the physiological symptoms, is reflected in negative impact on patient quality of life.[31] Alternative approaches

could be to use the prediction of imminent arrhythmia to prevent ventricular arrhythmia by high-rate pacing or over-drive suppression,[32] or to allow the possibility of automated drug administration.[33] Recent experimental studies have demonstrated that ICDs can be programmed to monitor BVR and initiate high-rate pacing to prevent torsades de pointes in animal models.[32]

BVR was also associated with appropriate therapy during follow-up in our patient cohort. In the multivariable analysis, pre-nsVT BVR was the strongest predictor of appropriate therapy, and was higher in patients who received appropriated therapy. The pre-nsVT BVR may reflect the degree of repolarization reserve and thus patients with lowest reserve would be most likely to develop sustained arrhythmia. Resting BVR is likely to be less informative because it does not provide insight into the repolarization under challenge.

## Limitations

In our study, the digital Holter recordings were recorded at a sampling frequency of 200 Hz, compared with experimental studies that were performed at 1000 Hz or more. Thus, this difference may have influenced the accuracy of BVR calculation, and should be considered when interpreting these data.

It is conceivable that BVR may increase without the occurrence of arrhythmia. The current technical challenges of automated fiducial point detection limit us from assessing BVR over the complete 24 hours of monitoring. We did, however, see stable values of BVR in our control patients without peaks in BVR at timepoints spread over the day.

Mortality in the patient cohort was low and a majority of these deaths occurred out-of-hospital and the cause was not ascertained. Therefore, an analysis of mortality was not performed. Future work could benefit from prospective longitudinal follow-up of patients to assess the long-term predictive value of BVR on arrhythmic death.

# CONCLUSIONS

BVR is increased in high-risk patients with ICM and DCM, suggesting a reduced repolarization reserve in these patients. BVR increases further immediately before nsVT, predicting imminent arrhythmia in patients with ICM as well as those with DCM. Real-time monitoring of BVR could possibly be used for predicting impending ventricular arrhythmia in high-risk patients.

## ARTICLE INFORMATION

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### Supplemental Material

Tables S1–S3
Figures S1–S6

## REFERENCES

1. Myerburg RJ, Interian A, Mitrani RM, Kessler KM, Castellanos A. Frequency of sudden cardiac death and profiles of risk. *Am J Cardiol*. 1997;80:10F–19F. doi: 10.1016/S0002-9149(97)00477-3
2. Gama F, Ferreira J, Carmo J, Costa FM, Carvalho S, Carmo P, Cavaco D, Morgado FB, Adragão P, Mendes M. Implantable cardioverter-defibrillators in trials of drug therapy for heart failure: a systematic review and meta-analysis. *J Am Heart Assoc*. 2020;9:e015177. doi: 10.1161/JAHA.119.015177
3. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2018;138:e272–e391. doi: 10.1161/CIR.0000000000000549
4. Nielsen JC, Lin YJ, de Oliveira Figueiredo MJ, Shamloo AS, Alfie A, Boveda S, Dagres N, Di Toro D, Eckhardt LL, Ellenbogen K, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on risk assessment in cardiac arrhythmias: use the right tool for the right outcome. *Europace*. 2020;22:1147–1148. doi: 10.1093/europace/euaa065
5. Wathen MS, Sweeney MO, Degroot PJ, Stark AJ, Koehler JL, Chisner MB, Machado C, Adkisson WO. Shock reduction using antitachycardia pacing for spontaneous rapid ventricular tachycardia in patients with coronary artery disease. *Circulation*. 2001;104:796–801. doi: 10.1161/hc3101.093906
6. Varma N, Cygankiewicz I, Turakhia MP, Heidbuchel H, Hu YF, Chen LY, Couderc JP, Cronin EM, Estep JD, Grieten L, et al. 2021 ISHNE/HRS/EHRA/APHRS expert collaborative statement on mHealth in arrhythmia management: digital medical tools for heart rhythm professionals: from the International Society for Holter and Noninvasive Electrocardiology/Heart Rhythm Society/European Heart Rhythm Association/Asia-Pacific Heart Rhythm Society. *Circ Arrhythm Electrophysiol*. 2021;14:234–283. doi: 10.1161/CIRCEP.120.009204
7. Thomsen MB, Verduyn SC, Stengl M, Beekman JDM, de Pater G, van Opstal J, Volders PGA, Vos MA. Increased short-term variability of repolarization predicts d-sotalol-induced torsades de pointes in dogs. *Circulation*. 2004;110:2453–2459. doi: 10.1161/01.CIR.0000145162.64183.C8
8. Tereshchenko LG, Cygankiewicz I, Mcnitt S, Vazquez R, Bayes-genis A, Han L, Sur S, Couderc J, Berger RD, De LAB. Predictive value of beat-to-beat QT variability index across the continuum of left ventricular

dysfunction: competing risks of noncardiac or cardiovascular death and sudden or nonsudden cardiac death. *Circ Arrhythm Electrophysiol*. 2012;5:719–727. doi: 10.1161/CIRCEP.112.970541
9. Smoczyńska A, Loen V, Sprenkeler DJ, Tuinenburg AE, Ritsema van Eck HJ, Malik M, Schmidt G, Meine M, Vos MA. 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. *J Am Heart Assoc*. 2020;9:1–9. doi: 10.1161/JAHA.120.018133
10. Vandenberk B, Garweg C, Voros G, Floré V, Marynissen T, Sticherling C, Zabel M, Ector J, Willems R. Changes in implantation patterns and therapy rates of implantable cardioverter defibrillators over time in ischemic and dilated cardiomyopathy patients. *Pacing Clin Electrophysiol*. 2016;39:848–857. doi: 10.1111/pace.12891
11. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary. *Heart Rhythm*. 2018;15:e190–e252. doi: 10.1016/j.hrthm.2017.10.035
12. Afsar N, Fak AS, Metzger JT, Van Melle G, Kappenberger L, Bogousslavsky J. Acute stroke increases QT dispersion in patients without known cardiac diseases. *Arch Neurol*. 2003;60:346–350. doi: 10.1001/archneur.60.3.346
13. Vandenberk B, Vandael E, Robyns T, Vandenberghe J, Garweg C, Foulon V, Ector J, Willems R. Which QT correction formulae to use for QT monitoring? *J Am Heart Assoc*. 2016;5:e003264. doi: 10.1161/JAHA.116.003264
14. Moeyersons J, Amoni M, Huffel SV, Willems R, Varon C. R-DECO: an open-source Matlab based graphical user interface for the detection and correction of R-peaks. *PeerJ Comput Sci*. 2019;5:1–20. doi: 10.7717/peerj-cs.226
15. Moeyersons J, Goovaerts G, Huijghebaert S, Vandenberk B, Willems R, Van Huffel S. Automated T wave end detection methods: comparison of four different methods for T wave end detection. Proceedings of the 10th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2017). 2017;4:92–98. Available at: https://www.scitepress.org/Papers/2017/61717/61717.pdf.
16. Black N, D'Souza A, Wang Y, Piggins H, Dobrzynski H, Morris G, Boyett MR. Circadian rhythm of cardiac electrophysiology, arrhythmogenesis, and the underlying mechanisms. *Heart Rhythm*. 2019;16:298–307. doi: 10.1016/j.hrthm.2018.08.026
17. Bas HD, Baser K, Hoyt J, Yokokawa M, Labounty T, Morady F, Bogun F. Effect of circadian variability in frequency of premature ventricular complexes on left ventricular function. *Heart Rhythm*. 2016;13:98–102. doi: 10.1016/j.hrthm.2015.07.038
18. Berger RD, Kasper EK, Baughman KL, Marban E, Calkins H, Tomaselli GF. Beat-to-beat QT interval variability: novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. *Circulation*. 1997;96:1557–1565. doi: 10.1161/01.CIR.96.5.1557
19. Hinterseer M, Beckmann B-M, Thomsen MB, Pfeufer A, Ulbrich M, Sinner MF, Perz S, Wichmann H-E, Lengyel C, Schimpf R, et al. Usefulness of short-term variability of QT intervals as a predictor for electrical remodeling and proarrhythmia in patients with nonischemic heart failure. *Am J Cardiol*. 2010;106:216–220. doi: 10.1016/j.amjcard.2010.02.033
20. Floré V, Claus P, Antoons G, Oosterhoff P, Holemans P, Vos MA, Sipido KR, Willems R. Microvolt T-wave alternans and beat-to-beat variability of repolarization during early postischemic remodeling in a pig heart. *Heart Rhythm*. 2011;8:1050–1057. doi: 10.1016/j.hrthm.2011.02.015
21. Brunner M, Zehender M, Koren G, Brunner M, Peng X, Liu GX, Ren X, Ziv O, Choi B, Mathur R, et al. Mechanisms of cardiac arrhythmias and sudden death in transgenic rabbits with long QT syndrome. *J Clin Invest*. 2008;118:2246–2259. doi: 10.1172/JCI33578
22. Varró A, Baczkó I. Cardiac ventricular repolarization reserve: a principle for understanding drug-related proarrhythmic risk. *Br J Pharmacol*. 2011;164:14–36. doi: 10.1111/j.1476-5381.2011.01367.x
23. Volders PGA, Sipido KR, Vos MA, Kulcsár A, Verduyn SC, Wellens HJJ. Cellular basis of biventricular hypertrophy and arrhythmogenesis in dogs with chronic complete atrioventricular block and acquired torsade de pointes. *Circulation*. 1998;98:1136–1147. doi: 10.1161/01.CIR.98.11.1136
24. Dries E, Amoni M, Vandenberk B, Johnson D, Gilbert G, Nagaraju CK, Puertas RD, Abdesselem M, Santiago DJ, Roderick HL, et al. Altered adrenergic response in myocytes bordering a chronic myocardial infarction underlies in vivo triggered activity and repolarization instability. *J Physiol*. 2020;598:2875–2895. doi: 10.1113/JP278839
25. Piacentino V. Cellular basis of abnormal calcium transients of failing human ventricular myocytes. *Circ Res*. 2003;92:651–658. doi: 10.1161/01.RES.0000062469.83985.9B
26. O'Rourke B, Kass DA, Tomaselli GF, Ka S, Tunin R, Marba E. Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, I: experimental studies. *Circ Res*. 1999;19:562–570. doi: 10.1161/01.RES.84.5.562
27. Akar FG, Spragg DD, Tunin RS, Kass DA, Tomaselli GF. Mechanisms underlying conduction slowing and arrhythmogenesis in nonischemic dilated cardiomyopathy. *Circ Res*. 2004;95:717–725. doi: 10.1161/01.RES.0000144125.61927.1c
28. Vrtovec B, Delgado R, Zewail A, Thomas CD, Richartz BM, Radovancevic B. Prolonged QTc interval and high B-type natriuretic advanced heart failure. *Circulation*. 2003;107:1764–1769. doi: 10.1161/01.CIR.0000057980.84624.95
29. Sachdev M, Fetics BJ, Lai S, Dalal D, Insel J, Berger RD. Failure in short-term prediction of ventricular tachycardia and ventricular fibrillation from continuous electrocardiogram in intensive care unit patients. *J Electrocardiol*. 2010;43:400–407. doi: 10.1016/j.jelectrocard.2010.02.005
30. Hasdemir C, Shah N, Rao AP, Acosta H, Matsudaira K, Neas BR, Reynolds DW, Po S, Lazzara R, Beckman KJ. Analysis of troponin I levels after spontaneous implantable cardioverter defibrillator shocks. *J Cardiovasc Electrophysiol*. 2002;13:144–150. doi: 10.1046/j.1540-8167.2002.00144.x
31. Kamphuis HCM, de Leeuw JR, Derksen R, Hauer RNW, Winnubst JAM. Implantable cardioverter defibrillator recipients: quality of life in recipients with and without ICD shock delivery: a prospective study. *Europace*. 2003;5:381–389. doi: 10.1016/S1099-5129(03)00078-3
32. Smoczyńska A, Loen V, Aranda A, Beekman DM, Meine M, Vos MA. High-rate pacing guided by short-term variability of repolarization prevents imminent ventricular arrhythmias automatically by an implantable cardioverter-defibrillator in the chronic atrioventricular block dog model. *Heart Rhythm*. 2020;17:2078–2085. doi: 10.1016/j.hrthm.2020.07.023
33. Raviele A, Brignole M, Menozzi C, Giada F, Dorigo A. Development of an implantable drug delivery system for the treatment of vasovagal syncope: a dream or a real Prospect? In: Raviele A, ed *Cardiac Arrhythmias*. Springer; 1997:422–427.

# SUPPLEMENTAL MATERIAL

**Table S1. Patient baseline characteristics of control patients without structural heart disease (ESUS group).**

| | | Control |
|---|---|---|
| n | | 50 |
| Age (years) | | 60 ± 12.5 |
| Sex | | |
| | Male (%) | 41 (82) |
| | Female (%) | 9 (18) |
| BMI | | 25.3 ± 4.3 |
| NYHA (%) | | |
| | 1 | 31 (59.6) |
| | 2 | 17 (32.7) |
| | 3 | 3 (5.8) |
| | 4 | 1 (1.9) |
| LVEF (%) | | 59.8 ± 9.7 |
| Indication (%) | | |
| | Primary | |
| | Secondary | |

| | | |
|---|---|---|
| History (%) | | |
| | Stroke/TIA | 14 (28.8) |
| | Diabetes | 9 (17.3) |
| | Atrial fibrillation | 1 (1.9) |
| | Hypertension | 29 (55.8) |
| Creatinine (mg/dL) | | 0.98 ± 0.30 |
| Medications (%) | | |
| | Beta-blocker | 12 (23.1) |
| | Statin | 26 (50.0) |
| | ACE-I/ ARB | 14 (26.9) |
| | Loop diuretic | 2 (3.8) |
| | MRA | 4 (7.7) |
| | Aspirin | 24 (46.2) |
| | VKA | 2 (3.8) |
| | NOAC | 1 (1.9) |
| | Amiodarone | 2 (3.8) |
| | Other AAD | 7 (13.4) |

ECG

| | |
|---|---|
| Heart rate (bpm) | 71.1 ± 16.1 |
| QRS (ms) | 113.3 ± 25.1 |
| QT (ms) | 404 ± 40.2 |
| QTc (ms) | 419 ± 26.3 |
| LBBB (%) | 2 (3.8) |
| RBBB (%) | 8 (16) |

Data expressed as n (%) or mean ± SD. ICM – ischemic cardiomyopathy, DCM – dilated cardiomyopathy, BMI – body mass index, NYHA – New York Heart Association classification of heart failure, LVEF – left ventricular ejection fraction, ACE-I – Angiotensin converting enzyme inhibitor / Angiotensin receptor blocker, MRA – mineralocorticoid receptor antagonist, VKA – vitamin K antagonist, NOAC – novel oral anticoagulant, AAD – anti-arrhythmia drug, bpm – beats/minute, LBBB – left bundle branch block, RBBB – right bundle branch block. Stroke/TIA defined as history of stroke/TIA prior to index admission.

ICD candidates had lower LVEF (ICM+nsVT: 28.6 ± 8.8%, DCM+nsVT: 27.3 ± 10.5%, ICM-nsVT: 28.1 ± 9.3%, DCM-nsVT: 29.7 ± 11.5% vs control: 59.8 ± 9.7%, $P$ <0.01) and higher New York Heart Association classification of heart failure (NYHA) with more

ICM+nsVT in class 1 than DCM+nsVT (34.9% vs DCM+nsVT: 21.6%, $P<0.05$). In addition, ICD candidates had longer QTc intervals (ICM+nsVT: 448 ± 41.8 ms, DCM+nsVT: 439 ± 37.1 ms, ICM-nsVT: 443 ± 33.9 and DCM-nsVT: 432 ± 42.9 vs control: 419 ± 26.3 ms) and more left bundle branch block (LBBB) compared to controls (ICM+nsVT: 25.6%, DCM+nsVT: 29.7%, ICM-nsVT: 18.5% and DCM-nsVT: 44.4%, vs 3.8%, $P<0.01$).

**Table S2. Holter electrophysiological parameters of control patients without structural heart disease (ESUS group).**

| | Control |
|---|---|
| n | 50 |
| Quality – | |
| % of Holter analyzed | 96.7 ± 2.1 |
| Heart rate (bpm) | 71.8 ± 11.9 |
| Bradycardia episodes | 2.5 (0-21.5) |
| Pauses | 0 (0-2) |
| Atrial extrasystoles per hr | 4.8 (0.9-32.4) |
| Ventricular extrasystoles per hr | 1.0 (0-4.5) |
| Non-sustained VT | |
| number of episodes | 0 |
| average rate (bpm) | N/D |
| average duration (s) | N/D |
| Sustained VT | |
| number of patients | 0 |

| | | |
|---|---|---|
| | average rate (bpm) | N/D |

Data expressed as n (%) or mean ± SD. Bpm – beats per minute, hr – hour, AV block – atrioventricular block episodes, VT – ventricular tachycardia.

ICD patients, both ICM and DCM patients had more extrasystoles than non-CVD controls (*P* = 0.0035 and 0.0391 respectively).

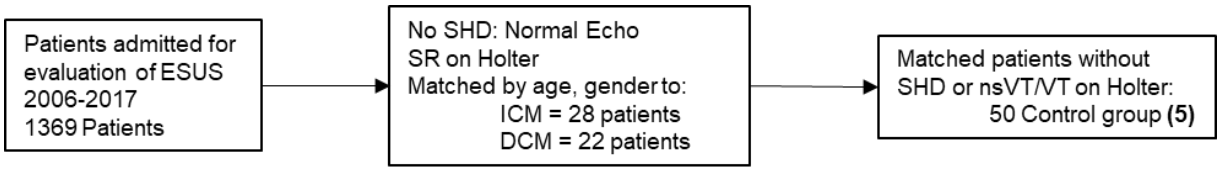
**Table S3. Characteristics of patients with and without appropriate ICD therapy**.

| Clinical variable | APT+ve | APT-ve | *P* value |
|---|---|---|---|
| N | 20 | 60 | |
| ICM | | | |
| % | 14 (73.6%) | 31 (50.8%) | 0.112 |
| Primary prophylaxis % | 15 (78.9%) | 52 9 (85.5%) | 0.496 |
| Sex | 16 (80.0%) | 49 (81.7%) | 0.998 |
| Age | 61.3 ± 11.1 | 58.1 ± 14.8 | 0.374 |
| LVEF | 30.7 ± 7.7 | 27.1 ± 9.9 | 0.152 |
| Atrial fibrillation | 2 (10.5%) | 4 (6.6%) | 0.613 |
| ECG | | | |
| Heart rate (bpm) | 66.9 ± 12.5 | 67.2 ± 13.97 | 0.935 |
| QRS (ms) | 123.4 ± 30.2 | 121.3 ± 28.4 | 0.778 |
| QT (ms) | 444.2 ± 60.8 | 426.0 ± 37.3 | 0.103 |
| Holter | | | |
| Ventricular extrasystoles | 252.3 ± 327.8 | 190.6 ± 325.6 | 0.470 |

| | | | |
|---|---|---|---|
| Number of nsVT episodes | 1.9 ± 1.3 | 1.2 ± 0.7 | 0.008 |
| BVR | | | |
| Rest | 1.7 ± 0.3 | 1.4 ± 0.3 | 0.019 |
| Max BVR | 2.6 ± 0.4 | 1.9 ± 0.5 | <0.001 |
| ∆ BVR | 0.9 ± 0.4 | 0.5 ± 0.4 | 0.003 |

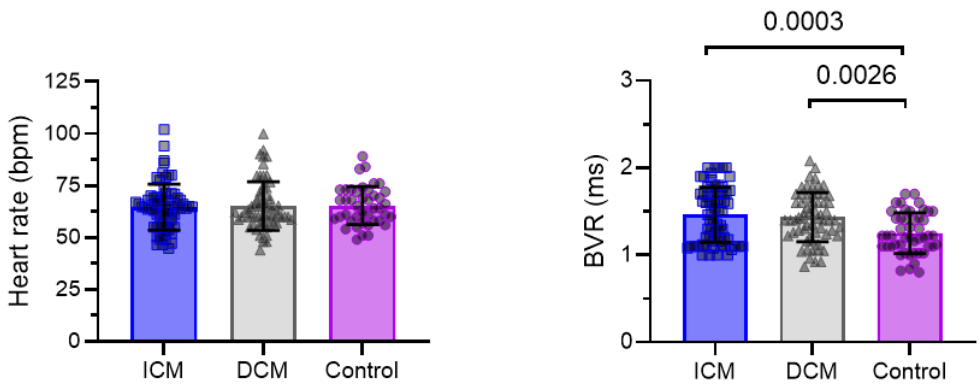
ICM – ischemic cardiomyopathy, LVEF – left ventricular ejection fraction, ECG – electrocardiogram, bpm – beats per minute, nsVT – non-sustained ventricular tachycardia, BVR – beat-to-beat variability of repolarization, max – maximum. Chi-squared test with Fisher's exact or two-tailed t-test.

**Figure S1. Experimental design.**



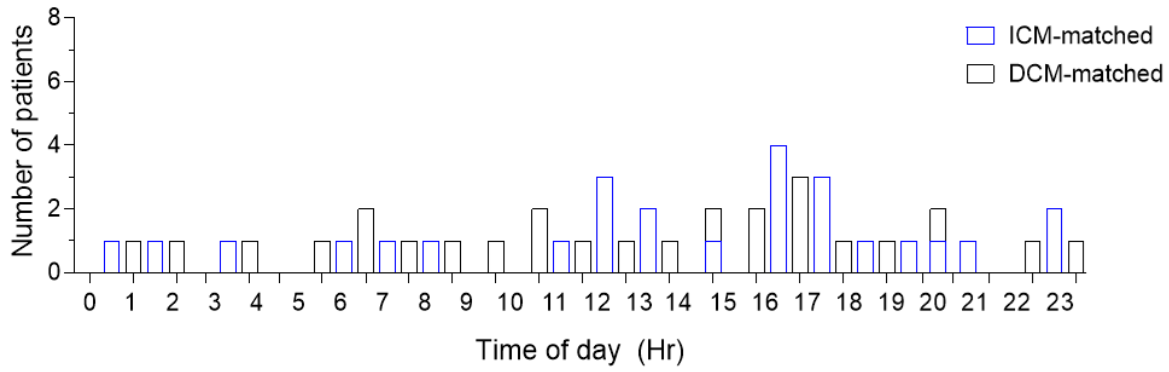

Study flow chart illustrating patient inclusion of matched control patients without structural heart disease. Patients admitted for evaluation of embolic stroke of undetermined source (ESUS) in 2006-2017 were considered. Patients with a Holter recording were matched to ICM (28) and DCM (22) patients from the ICD candidates with nsVT on Holter. SHD – structural heart disease, SR – sinus rhythm, nsVT – non-sustained ventricular tachycardia.

**Figure S2. Beat-to-beat variation of repolarization (BVR) at rest.**



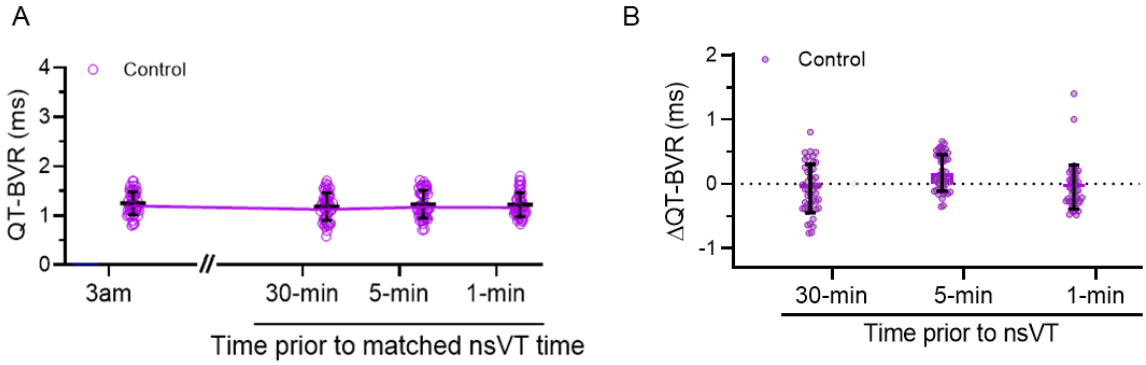

Summary data of baseline heart rate (left) and QT-BVR (right) of control, ICM and DCM patients taken at 3:00am. N = 72 ICM, 63 DCM and 50 Control.1-way ANOVA with Bonferroni post hoc analysis. *$P < 0.05$, **$P < 0.01$ vs Control,

**Figure S3. Distribution of matched nsVT timepoint in control patients.**




Time of day of the ICM/DCM-matched timepoint of nsVT used for analysis, notably similar to the profile seen in Fig. 2.

**Figure S4. Temporal changes in BVR at matched timepoints in control patients without structural heart disease.**

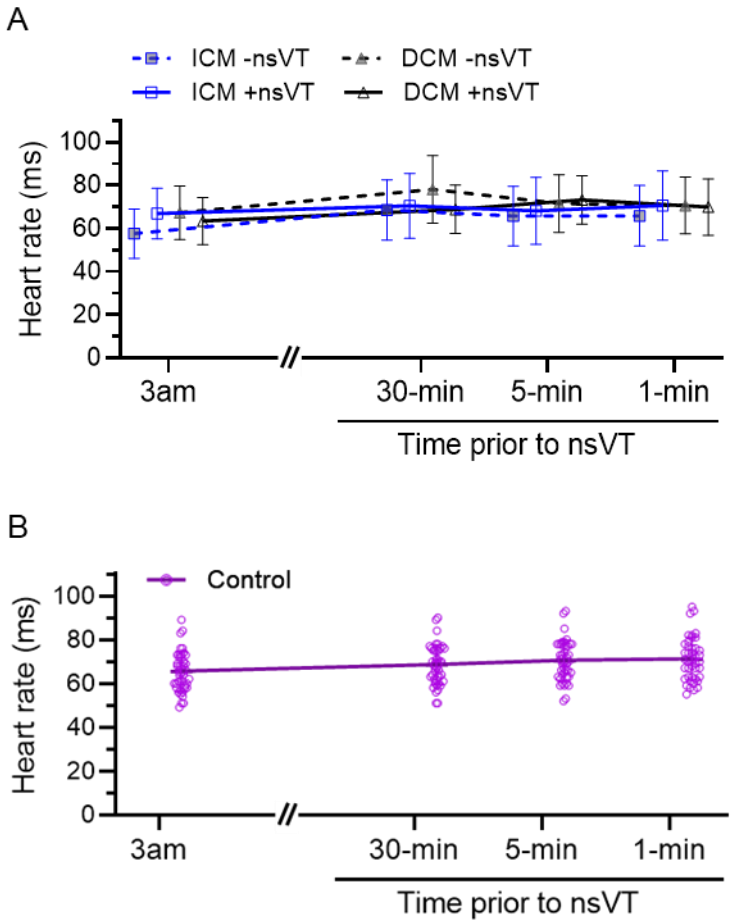



**A,** Summary data of temporal changes in QT-BVR of control patients. Timepoints are matched to nsVT timepoints of ICD patients in Figure 4.

**B,** Summary data of the change in BVR between timepoints presented in A.

N = 50 patients. Mixed effects model analysis with Bonferroni post hoc correction.

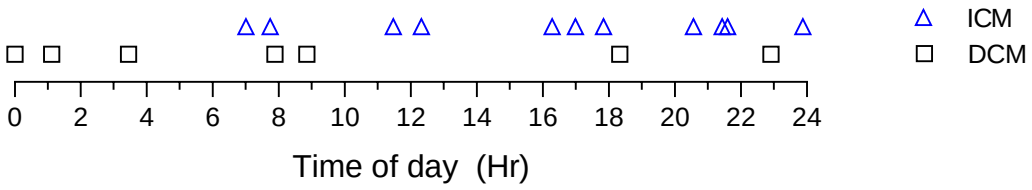
**Figure S5. Temporal changes in heart rate in relation to nsVT.**




**A,** Mean data of the temporal changes in heart rate at rest and prior to nsVT, comparing the groups and timepoints. Mixed effects model with Bonferroni post hoc correction. N = 72 ICM, 63 DCM and 50 Control.

**B,** Summary of the temporal changes in heart rate at rest and prior to nsVT. Repeated measures ANOVA with Bonferroni post hoc. N = 50 patients.

**Figure S6. Occurrence of the second non-sustained ventricular tachycardia (nsVT) episode.**




Time of occurrence during the day of the second nsVT considered for analysis that was at least 1 hour after the index nsVT presented in fig. 2A