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

Agnieszka Smoczyńska, MD,* Vera Loen, MD,* Alfonso Aranda, MSc,† Henriëtte D.M. Beekman,* Mathias Meine, MD, PhD,‡ Marc A. Vos, PhD*

From the *Department of Medical Physiology, Division Heart and Lungs, University Medical Center Utrecht, Utrecht, The Netherlands, †Medtronic Bakken Research Center, Maastricht, The Netherlands, and ‡Department of Cardiology, Division Heart and Lungs, University Medical Center Utrecht, Utrecht, The Netherlands.

BACKGROUND The anesthetized, complete chronic atrioventricular block (CAVB) dog model allows reproducible inducibility of torsades de pointes (TdP) arrhythmias due to ventricular remodeling and after a challenge with an Ik, blocker. High-rate pacing (HRP) prevents ventricular arrhythmias but has long-term detrimental effects on cardiac function when applied continuously. Temporal dispersion of repolarization, quantified as short-term variability (STV), increases before ventricular arrhythmias and has been proposed as a marker to guide HRP.

OBJECTIVE The purpose of this proof-of-principle study was to show that automatically determined STV can guide HRP to prevent imminent ventricular arrhythmias.

METHODS Eight CAVB dogs were implanted with an implantable cardioverter-defibrillator (ICD) with software to automatically determine STV (STVICD) in real time. During HRP, STV was measured offline from right ventricular (RV) electrograms (EGMs) and left ventricular (LV) monophasic action potential durations (MAPDs) (STVRV,EGM/LV,MAPD). The CAVB dogs were challenged twice with dovetilide (0.025 mg/kg intravenously over 5 minutes or until the first TdP). In experiment 1, the individual STVICD threshold before the first arrhythmic event was determined and programmed into the ICD. In experiment 2, HRP with 100 bpm was initiated automatically once the STVICD threshold was reached.

RESULTS In experiment 1, 8 of 8 dogs had repetitive TdP, and STVICD increased from 0.96 ± 0.42 ms to 2.10 ± 1.26 ms (P<.05). In experiment 2, all dogs reached the STV threshold. HRP decreased STV before RV, EGM/LV, MAPD from 2.02 ± 1.12 ms to 0.78 ± 0.28 ms, which was accompanied by prevention of TdP in 7 of 8 dogs.

CONCLUSION STV can guide HRP automatically by an ICD to prevent ventricular arrhythmias.

KEYWORDS High-rate pacing; Repolarization; Short-term variability; Torsades de pointes

Introduction

The implantable cardioverter-defibrillator (ICD) has gained a pivotal role in the management of ventricular arrhythmias since landmark trials showed improvement in primary and secondary prevention of sudden cardiac death. In addition to defibrillation functionality, the ICD can pace the heart at higher rates than sinus rhythm to prevent ventricular arrhythmias. This form of arrhythmia management is not preferred because permanent pacing has long-term detrimental effects on cardiac function when applied continuously. Therefore, it is indicated only in patients with high-risk congenital long QT syndrome or those with proven sustained pause-dependent ventricular arrhythmias. In order to make use of the antiarrhythmic efficacy of high-rate pacing (HRP) without the concomitant possibility of heart failure, HRP should be applied only temporarily in the presence of increased arrhythmic risk.

Temporal dispersion of repolarization, quantified as short-term variability (STV), has been proposed as the
electrophysiological marker for continuous monitoring of imminent arrhythmic risk. In the complete chronic atrioventricular block (CAVB) dog model with an enhanced susceptibility to torsades de pointes (TdP) arrhythmias, previous studies demonstrated that STV, which reflects repolarization reserve, increased before an arrhythmic event induced by a proarrhythmic drug. This increase in STV occurred before the first sign of ventricular arrhythmia, which usually consists of single ectopic beats (sEB) and multiple ectopic beats (mEB), thus providing sufficient time to initiate antiarrhythmic therapy. HRP at VVI100 reduced STV and effectively prevented TdP in CAVB dogs. In the present proof-of-principle study, the efficacy of automated HRP guided by STV to prevent TdP in the CAVB dog model was evaluated.

**Methods**

Animal handling was in accordance with the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes and with Dutch law, laid down in the Experiments on Animals Act. All experiments were performed with approval of the Central Authority for Scientific Procedures on Animals.

**Animal preparation**

Eight adult, purpose-bred mongrel dogs (3 female and 5 male; body weight 24 ± 4 kg) (Marshall, NY, USA) were used. Experiments were performed with the animals under general anesthesia with mechanical ventilation at 12 breaths per minute. Premedication consisted of methadone 0.5 mg/kg, acepromazine 0.5 mg/kg, and atropine 0.02 mg/kg intramuscular (IM). General anesthesia was induced with 25 mg/kg pentobarbital intravenous (IV) and maintained by isoflurane 1.5% in a mixture of O₂ and N₂O (1:2). Antibiotics (ampicillin 1000 mg IV preoperatively; ampicillin 1000 mg IM postoperatively) and analgesics (Meloxicam 0.2 mg/kg subcutaneously preoperatively; buprenorphine 0.3 mg IM postoperatively) were administered. During the initial procedure, the proximal bundle of His was ablated with radiofrequency energy to create complete AV block. An Evera ICD (Medtronic) with a lead (quadripolar, dual-shock coil) in the right ventricular (RV) apex was implanted via the right jugular vein under fluoroscopic guidance. The animals were left to remodel for 3 weeks in idioventricular rhythm (IVR).

**Experimental protocol**

Two serial experiments were performed in IVR: (1) an inducibility experiment and (2) a prevention experiment (Figure 1). For animal safety, dogs were paced with VVI40–50 when they had IVR ≤30 bpm. The ICD was equipped with an algorithm to automatically determine STV in real time (monitoring in both experiments) and to initiate HRP based on STV (prevention experiment only).

Ten surface electrocardiographic (ECG) leads (6 limb, 4 precordial) were recorded. Due to the limited storage capacity of the ICD, EGM recordings could only be saved in the internal memory of the ICD for 480 beats, whereas all generated STV values could be stored. For offline confirmation of the results obtained with the ICD, endocardial unipolar EGM recordings were acquired with a duodecapolar catheter (St. Jude Medical, St. Paul, MN). Under fluoroscopic guidance, the catheter was placed in the apex of the RV in proximity to the ICD lead via the femoral vein. A reference electrode was placed in the right hind leg vein. A monophasic action potential (MAP) catheter (Hugo Sachs Elektronik GmbH, March, Germany) was placed in the left ventricular (LV) apex via the femoral artery.

In the first experiment, the inducibility experiment (Figure 1A), susceptibility to TdP was tested with the IKr blocker dofetilide (0.025 mg/kg IV infused over 5 minutes or until the first TdP occurred). The STV monitoring algorithm was activated in the ICD to determine the change in STV preceding the arrhythmias. The arrhythmic outcome was monitored for 10 minutes from the start of dofetilide infusion. An animal was considered to be inducible when ≥3 TdPs occurred, which was defined as ≥5 ventricular beats with the QRS vector twisting around the isoelectric line. For animal safety, defibrillation was applied via external patches if TdP did not self-terminate within 10 seconds. To assess the pacing rate necessary to suppress TdP, pacing with VVI60, VVI80, and VVI100 was initiated 10 minutes after the start of dofetilide infusion. Each pacing rate was applied for 1–2 minutes.

In the second experiment, the prevention experiment (Figure 1B), the animals were challenged with dofetilide again. The same dose and infusion time of dofetilide were used as in the inducibility experiment per individual animal. The prevention algorithm was activated in the ICD, that is, HRP was started when the individually predetermined STV threshold was reached. RR interval was automatically decreased by 30 ms/s by the ICD until the target heart rate of VVI100. The arrhythmic outcome was monitored for 10 minutes from the start of dofetilide infusion. After 10 minutes of VVI100, the pacing rate was automatically decreased by increasing the RR interval by 10 ms/s. The arrhythmic outcome after cessation of HRP was evaluated until 20 minutes after the start of dofetilide infusion.

**Data analysis**

All arrhythmias consisting of sEB, mEB, and TdP were scored during the 10 minutes after the start of dofetilide...
infusion. An EB was counted when it occurred during the T wave of the previous beat. The arrhythmia score (AS) was calculated as the average of the 3 most severe arrhythmic events during the 10 minutes from the start of dofetilide infusion.\textsuperscript{13,14} In order to compare AS during HRP at different frequencies in the inducibility experiment, AS was quantified over the last minute of IVR and the first minute of each pacing frequency.

Surface ECG, RV EGM, and LV MAP signals were recorded using EP-TRACER (Cardiotek, Maastricht, The Netherlands) at a sampling frequency of 1 kHz for offline measurements. RR and QT intervals were measured on ECG lead II in EP-TRACER. The QT interval was corrected (QTc) for heart rate according to the Van de Water formula.\textsuperscript{15} Custom-made software (AutoMAPD, MATLAB, Mathworks, Natick, MA) was used to determine the activation recovery interval on the RV EGM from the minimum $dV/dt$ of the QRS complex to the maximum $dV/dt$ of the T wave, irrespective of T-wave morphology, and to calculate STV\textsubscript{RV,EGM}. LV monophasic action potential duration (MAPD) was determined from the initial peak until 80% of repolarization for calculation of STV\textsubscript{LV,MAPD}.

For calculation of STV by the ICD (STV\textsubscript{ICD}), the determinant of repolarization was measured from the moment of ventricular sensing by the standard Medtronic technique until T-wave end. Upon ventricular sensing, a fixed window of 700 ms was set to assess the signal by the algorithm. The QRS was blanked according to the manually measured width (120–160 ms). From the resulting signal, T-wave end was determined as 60% of the area under the curve of the first derivative of the T wave.\textsuperscript{12}

STV was calculated from 31 consecutive beats as $\sum |D_{n+1} - D_n|/(30 \times \sqrt{2})$, where D represents the determinant of repolarization. All reported measurements were performed at baseline and after administration of dofetilide before the first arrhythmic event, irrespective of whether it fell in the T wave of the previous beat. During HRP, only STV\textsubscript{RV,EGM} and STV\textsubscript{LV,MAPD} were measured offline at 2 minutes of VVI100 during the inducibility experiment and at 10 minutes of VVI100 during the prevention experiment.

**Statistical analysis**

Numerical values are given as mean ± SD. Comparison of serial data was performed with a paired Student $t$ test, or with repeated measurement 1-way analysis of variance with Tukey correction for multiple comparisons. Simple linear regression was used to compare different STV measurement modalities. Statistical analyses were performed using Prism 8.0 (GraphPad Software Inc, La Jolla, CA). $P < .05$ was considered significant.

**Results**

The experiments were performed in IVR in 5 of 8 animals. Three dogs required pacing of 43 ± 6 bpm. STV\textsubscript{ICD} was comparable to STV\textsubscript{RV,EGM} (Pearson $r^2 = 0.75$; $P < .001$). Table 1 summarizes the electrophysiological parameters during the inducibility and prevention experiments. RR, QT, QTc, and STV\textsubscript{ICD} were similar at baseline during both experiments.

**Experiment 1**

Inducibility rate and determination of STV threshold

During the inducibility experiment, all animals were susceptible to repetitive TdP ($\geq 3$). The first arrhythmic event occurred 134 ± 49 seconds after the start of dofetilide infusion and was preceded by a prompt increase in STV\textsubscript{ICD} from 0.96 ± 0.42 ms to 2.10 ± 1.26 ms ($P < .05$) (Figure 2A). A representative STV depicted in a Poincaré plot (Figure 2B) shows that STV\textsubscript{RV,EGM} increased from 1.39 to 4.72 ms.

Of the 8 animals, the first arrhythmic event was sEB in 6 (Figure 2C), mEB in 1, and sudden-onset TdP in 1 (Figure 2D). There was a high variability in the duration.

![Diagram A](image1.png)

**Diagram A**

A schematic overview of the experimental protocol. Two serial experiments were performed: the inducibility experiment (A) and the prevention experiment (B). HRP = high-rate pacing; ICD = implantable cardioverter-defibrillator; IVR = idioventricular rhythm; STV = short-term variability.
between the first sEB/mEB and the first TdP occurrence (mean 120 ± 118 seconds; range 2–281 seconds). The interindividual variation in STV values and progression of the arrhythmic outcome were cause to individually determine the STV threshold to start the intervention during the prevention experiment. The RR interval at baseline was 1381 ± 281 ms, so it would take 26 seconds to reach the target RR interval of 600 ms when RR is gradually decreased by 30 ms/s by the ICD. The threshold for STV in the inducibility experiment, and before the start of high-rate pacing (HRP) based on short-term variability (STV) during the prevention experiment. STV in the inducibility experiment is only reported for the 7 animals without torsades de pointes.

Prevention experiment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Doftetilde</th>
<th>HRP VVI100</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>1381 ± 281</td>
<td>1351 ± 266</td>
<td>601 ± 0*†</td>
</tr>
<tr>
<td>QRS</td>
<td>108 ± 23</td>
<td>109 ± 22</td>
<td>120 ± 12</td>
</tr>
<tr>
<td>QT</td>
<td>469 ± 89</td>
<td>568 ± 63*</td>
<td>448 ± 39</td>
</tr>
<tr>
<td>QTc</td>
<td>433 ± 77</td>
<td>538 ± 61*</td>
<td>482 ± 39†</td>
</tr>
<tr>
<td>STV&lt;sub&gt;ICD&lt;/sub&gt;</td>
<td>0.96 ± 0.42</td>
<td>2.10 ± 1.26*</td>
<td>1.53 ± 0.96†</td>
</tr>
<tr>
<td>STV&lt;sub&gt;RV,EGM/LV,MAPD&lt;/sub&gt;</td>
<td>1.33 ± 0.51</td>
<td>2.74 ± 1.57*</td>
<td>600 ± 0*†</td>
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</tbody>
</table>

Values are given as mean ± SD. Data (in milliseconds) are given for before (baseline) and after doftetilde administration but before the first arrhythmic event in animals that had sudden-onset TdP during the inducibility experiment, and before the start of high-rate pacing (HRP) based on short-term variability (STV) during the prevention experiment. STV<sub>RV,EGM</sub> at VVI100 during the prevention experiment is only reported for the 7 animals without torsades de pointes.

EGM = electrogram; ICD = implantable cardioverter-defibrillator; LV = left ventricle; MAPD = monophasic action potential duration; QTc = corrected QT; RV = right ventricle.

*P <.05 vs baseline. †P <.05 vs doftetilde.

Serial measurement on RV EGM in 5 animals and on LV MAPD in 3 animals.

Determination of pacing frequency of HRP

Ten minutes after the start of doftetilde infusion, the pacing frequency to effectively suppress ventricular arrhythmias was determined. A representative of the arrhythmic outcome at each pacing rate is shown in Figures 3A–3C. AS of the 8 animals is shown in Figure 3D. At VVI60, 8 of 8 animals had repetitive TdP resulting in AS of 21 ± 13, whereas VVI80 decreased AS to 6 ± 6. All TdPs were suppressed at VVI100 in 8 of 8 animals and almost all ectopy was eliminated, resulting in a low AS of 1 ± 1. During HRP, STV was determined on the RV EGM in 5 dogs and on the LV MAPD in 3 dogs (STV<sub>RV,EGM/LV,MAPD</sub>) because of dislocation of either of the catheters as a result of repetitive defibrillations. The catheters were not moved back to the optimal position because mechanical manipulation of the endocardium may provoke ventricular arrhythmias that would have influenced the results. Moreover, previous studies showed a good correlation between STV derived from the EGM and from the MAP.

HRP at VVI100 decreased STV<sub>RV,EGM/LV,MAPD</sub> from 2.74 ± 1.57 ms to 1.53 ± 0.96 ms (P <.05) (Figure 3E). STV could not be determined at VVI60 and VVI80 due to ectopy and TdP. Therefore, the optimal pacing frequency for HRP was 100 bpm and was applied during the prevention experiment.

Experiment 2

Antiarrhythmic efficacy of STV-guided HRP

All animals reached the predetermined STV threshold during the prevention experiment after 129 ± 51 seconds, and the target heart rate of 100 bpm was reached 32 ± 10 seconds later (Figure 4). This was accompanied by a decrease in QTc from 519 ± 66 ms to 473 ± 36 ms, and a decrease in STV<sub>RV,EGM</sub> from 2.02 ± 1.12 ms to 0.78 ± 0.28 ms (both P <.05) (Table 1 and Figure 5A). A representative example of a Poincaré plot before the start of HRP and at 10 minutes of HRP is shown in Figure 5B. HRP at VVI100 prevented the occurrence of (repetitive) TdP in 7 of 8 animals (Figure 5C and Supplemental Video 1). From these 7 animals, 2 had short TdPs during the 32 seconds that was necessary to gradually increase the heart rate. One of these animals was the same one that had sudden-onset TdP during the inducibility experiment. Nevertheless, AS from the start of doftetilde infusion until 10 minutes of HRP at VVI100 decreased significantly from 54 ± 10 in the inducibility experiment to 15 ± 20 in the prevention experiment in the 8 animals (Figure 5D). HRP at VVI100 was insufficient to prevent TdP in 1 of 8 dogs; therefore, heart rate was manually increased to VVI110, which was sufficient to suppress TdP. Offline analysis revealed that STV<sub>RV,EGM</sub> still was
elevated from 0.88 ms at baseline to 2.44 ms during VVI100, whereas VVI110 decreased STVRV,EGM to 0.86 ms. After cessation of HRP, 8 of 8 dogs showed recurrent TdP, confirming that the dose of dofetilide was sufficient to cause a proarrhythmic state.

Discussion
This proof-of-principle study confirms 3 earlier findings but now with use of an ICD equipped with an algorithm to automatically determine STV and activate HRP once the STV threshold is reached: (1) ventricular arrhythmias are preceded by an increase in STV; (2) HRP is highly effective in preventing ventricular arrhythmias and can be guided by STV; and (3) HRP achieves prevention by decreasing the repolarization parameter STV.

Continuous monitoring of repolarization reserve for imminent proarrhythmic risk
Evidence presented over the years has indicated that the STV increase preceding arrhythmias occurs under both anesthetized and awake circumstances in the dog and in active humans, and it is not limited to a specific drug but is seen after administration of numerous proarrhythmic drugs in dogs and in humans.\textsuperscript{5-7,9,16} A variety of repolarization parameters in different recording methods can be used for determination of STV. MAPD has long been the gold standard for the measurement of STV \textit{in vitro} and \textit{in vivo}. However, its clinical utilization was limited due to the use of different recording modalities such as ECG and EGM in patients. The EGM leads of ICD signals are most suitable for continuous monitoring of proarrhythmic risk in an ambulatory setting. Previous studies have shown that STV derived from the activation recovery interval on the EGM is a reliable surrogate for MAPD using offline semiautomated measurements.\textsuperscript{9} This study shows that the automated methodology can be used for continuous monitoring of STV by the ICD in real time. The similar values of STV at baseline and the comparable change in STV preceding ventricular arrhythmias highlight the reproducibility of this methodology. It also confirms the high specificity of STV in distinguishing a proarrhythmic from a nonarrhythmic state. Hence, this methodology can be used for continuous monitoring of imminent proarrhythmic risk.

Efficacy of HRP
HRP can effectively prevent imminent ventricular arrhythmias. Oosterhoff et al\textsuperscript{11} reported a 71% reduction...
of inducibility rate in CAVB dogs paced at VVI100–110 compared to VVI60–70. These animals had HRP from the start of dofetilide administration. Wijers et al.10 started HRP after the first sEB occurred upon dofetilide administration and demonstrated that the increase in STV preceding arrhythmias could guide the initiation of HRP while preserving antiarrhythmic effectiveness at 70%. In the present study, STV-guided HRP reduced the inducibility rate by 88%. Pacing with VVI100 suppressed all arrhythmias in the inducibility experiment, whereas 1 of 8 dogs still had TdP during HRP at VVI100 in the prevention experiment. This particular dog had a higher QTc of 428 ms at baseline during the prevention experiment compared to 328 ms during the inducibility experiment. We

Figure 3  Effect of different pacing rates on ventricular arrhythmias and short-term variability (STV). During the inducibility experiment, 10 minutes after dofetilide infusion, torsades de pointes still occurs at VVI60 (A), frequent ectopy is present at VVI80 (B), and all torsades de pointes and ectopy are suppressed at VVI100 (C). D: Quantification of effect on arrhythmia score by high-rate pacing (HRP) during the last minute of idioventricular rhythm (IVR) and the first minute of each pacing frequency. E: HRP at VVI100 counteracts the increase in STV by dofetilide administration. Values are given as mean ± SD. *P < .05 vs IVR. †P < .05 vs VVI60. BL = baseline; EGM = electrogram; LV = left ventricle; MAPD = monophasic action potential duration; RV = right ventricle.

Figure 4  Representative electrocardiogram of the gradual increase in pacing rate by decreasing the cycle length by 30 ms/s. Horizontal arrows indicate the cycle length (in milliseconds). Vertical arrow indicates start of pacing.
hypothesize that conditions that are not controlled by the experiments (e.g., electrolyte balance) changed during the 4 weeks between the inducibility and prevention experiments, thus necessitating a higher pacing rate of VVI110.

**Antiarrhythmic mechanism of HRP**

Multiple mechanisms contribute to the antiarrhythmic properties of HRP. HRP decreases both temporal and spatial dispersion of repolarization. This is reflected as QTc shortening, decrease in STV, and suppression of early afterdepolarizations, in contrast to the decrease of interventricular dispersion, Tpeak-Tend, and spatial dispersion of repolarization. The antiarrhythmic property of HRP related to temporal dispersion of repolarization should be sought in the physiology of APD rate adaptation. In this study, repolarization parameters such as STV and QTc decrease after gradual increase of heart rate and coincide with the prevention of ventricular arrhythmias. A sudden change in heart rate from VVI60 to VVI100 was proarrhythmic in the study by Wijers et al., which indicates that time is needed for HRP to accelerate repolarization and facilitate the higher heart rate. The diastolic interval is shorter at higher heart rates, so there is less time for diastolic deactivation of IKs. In guinea pigs this results in incomplete deactivation of IKs and shortening of APD. In contrast, IKr activation is independent of the diastolic interval but has been linked to the repolarization rate, whereby a faster repolarization rate gives rise to a higher IKr, forming a positive feedback loop in which IKr further accelerates the repolarization rate. Experiments with selective ion channel blockers and activators have elucidated the contribution of these 2 delayed rectifier potassium currents to temporal dispersion of repolarization. IKr block increases STV in isolated canine ventricular myocytes and in vivo rabbit hearts. Blocking IKs in isolated canine cardiomyocytes also leads to an increase in STV. Beat-to-beat variability of repolarization decreases by activation of IKr and IKs, which suggests that the delayed rectifier potassium channels involved in the physiological rate adaptation of APD also strengthen the repolarization reserve.

**Clinical implications**

STV-guided HRP has the potential to shift device-based management of ventricular arrhythmias from termination to prevention, especially in patients with repolarization-dependent ventricular arrhythmias occurring in congenital and acquired long QT syndrome, in those with bradycardia and pause-dependent ventricular arrhythmias, and in patients with structural heart disease. HRP should be used...
with caution in patients with coronary artery disease due to the increased metabolic demand at higher heart rates. Initially, STV-guided HRP should be complementary to current ICD therapy to minimize shocks and thereby improve quality of life, while preserving the survival benefit of an ICD. This seems feasible given the possibility of adding this methodology to an ICD rather than replacing the defibrillation function.

**Study limitations**
These experiments were performed under controlled and stable conditions with the animals under anesthesia, in an animal model with complete AV block. Therefore, the influence of sinus rate changes and premature atrial complexes was not taken into account. The dogs likely were free of coronary artery disease, so the results should not be readily extrapolated to patients at risk for ventricular arrhythmias induced by acute ischemia. The automated algorithm could not monitor STV during HRP due to the fixed window width (700 ms) that exceeded the pacing cycle length (600 ms), which causes interference with the next QRS complex in the T-wave end determination. A shorter window width cut off the T-wave end in half of the animals due to the long QT phenotype and additional QT prolongation during dovetilide infusion. A dynamic window that shortens in length during a shorter RR interval would allow the device to reliably measure STV during HRP.

**Conclusion**
STV-guided HRP is highly effective in preventing TdP in the CAVB dog model. The fully automatic method for monitoring STV by the ICD is reliable and reproducible in predicting imminent ventricular arrhythmias. HRP strengthens the repolarization reserve, reflected as normalization of STV, which contributes to the antiarrhythmic effect.

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**Appendix**
**Supplementary data**
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrrthm.2020.07.023.

**References**