Proarrhythmic electrical remodelling is associated with increased beat-to-beat variability of repolarisation

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Received 3 July 2006; received in revised form 30 October 2006; accepted 20 November 2006

Time for primary review 16 days

Abstract

Objective: Acquired long-QT syndrome in combination with increased beat-to-beat variability of repolarisation duration (BVR) is associated with lethal torsades de pointes arrhythmias (TdP) in dogs with remodelled heart after atrioventricular block (AVB). We evaluated the relative contributions of bradycardia and ventricular remodelling to proarrhythmic BVR with and without pharmacological I_{Kr} block in order to identify the individual at risk.

Methods: Three groups of dogs were used: sinus rhythm dogs (n=12), dogs with acute AVB (n=8), and dogs with >3 weeks chronic AVB (n=27). Under anaesthesia, ECG and monophasic action potential duration (MAPD) were measured. Local BVR was quantified as short-term variability from 30 consecutive left ventricular MAPD (STV = \sum |D_{n+1} - D_{n+1}|/[30 \times \sqrt{2}]). All dogs received dofetilide iv.

Results: The slower ventricular rate acutely after AVB affected neither QTc nor STV (288±18 to 293±38 ms and 0.7±0.1 to 0.7±0.1 ms, respectively; P=NS for both), whereas ventricular remodelling increased both (to 376±46 and 2.3±0.6 ms, respectively; P<0.05 for both). Neither dogs in sinus rhythm nor acute AVB showed any TdP, whereas dofetilide induced TdP in 74% of the chronic-AVB dogs. Dofetilide increased the QTc interval in all groups (19–24%; P<0.05 for all groups), whereas STV was elevated in chronic-AVB dogs only (to 4.2±1.5 ms; P<0.05) and further confined to inducible chronic-AVB dogs (5.0±0.8 versus 1.9±0.4 ms for resistant dogs; P<0.05). Variability of the idioventricular rate was increased directly after AVB and did not influence BVR.

Conclusions: Under drug-free circumstances, a persistent high BVR in chronic-AVB dogs is remodelling dependent rather than a direct consequence of bradycardia acutely after AVB. Dofetilide causes a transient increase in BVR only in proarrhythmic dogs. Thus, BVR may aid the identification of the TdP-susceptible patient.

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Keywords: ECG; Heart-rate variability; Remodelling; Repolarisation; Ventricular arrhythmias

1. Introduction

Torsades de pointes arrhythmia (TdP) is a serious ventricular polymorphic tachycardia, which may herald fatal ventricular fibrillation and sudden death. By definition, the arrhythmia is associated with a prolonged QT interval of the ECG [1]. Drug-induced TdP can be induced by various pharmacological medications, but occurs almost exclusively in patients with an underlying cardiac pathology elevating their vulnerability to repolarisation-dependent arrhythmias [2,3]. Instead of prohibiting beneficial medical treatments to avoid drug-induced TdP, identification of the vulnerable patient could be an advantageous strategy [4].

Recently, several studies have concluded that QT prolongation on its own is not a reliable predictor of drug-induced TdP, whereas alternative or additional surrogate parameters have been proposed [5–8]. We have suggested
temporal beat-to-beat variability of repolarisation duration (BVR) as a candidate parameter [5]. Our research was performed in anaesthetised dogs with chronic atrioventricular block (AVB), with a ~70% incidence in TdP provoked by class-III antiarrhythmic drugs [9,10]. This enhanced susceptibility results from ventricular remodelling following the onset of chronic bradycardia [11,12]. The electrophysiological fraction of the remodelling processes features primarily a heterogeneous prolongation of repolarisation duration manifested by QTc prolongation in vivo. Furthermore, a chronically increased BVR is observed at baseline [13]. In this model, baseline BVR has been successfully employed to identify predisposition of individual animals: those showing large BVR die suddenly in the absence of anaesthesia and drugs [13].

In the present study, we evaluate the relative contributions of bradycardia and ventricular electrical remodelling to the persistently increased baseline BVR present in anaesthetised chronic-AVB dogs. Furthermore, we analyse the influence of physiological heart-rate variability on BVR and the response of BVR to pharmacological If block. Finally, we compared values of BVR in dogs with and without drug-induced proarrhythmia.

2. Methods

The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health and is in accordance with the European Directive for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (86/609/EU). The local animal-care committees of Maastricht and Utrecht Universities approved all experiments.

2.1. General

Experiments from 47 mongrel dogs of either sex were included in this investigation. 12 Experiments in dogs in sinus rhythm and 9 experiments in dogs in chronic AVB have been reported upon previously [9,10], whereas 11 chronic-AVB dogs are part of ongoing pharmacological studies on novel experimental drugs, where dofetilide serves as reference drug for proarrhythmia. BVR has not been reported for any of these dogs previously. Generally, inclusion criteria were: (1) anaesthesia induced by sodium pentobarbital (25 mg/kg i.v.) and maintained by 0.5% halothane in a mixture of O2 and N2O (1:2); (2) high quality recordings of monophasic action potentials (MAP, EP technologies, CA) from the left (LV) and right ventricle (RV); and (3) administration of 25 μg/kg dofetilide i.v. over 5 min.

Steerable MAP recording catheters were placed under fluoroscopic guidance at the endocardium of each ventricle. Endocardial location was selected based on MAP amplitude and reproducibility. In all experiments, 6 ECG leads from the limbs and the 2 MAPs were recorded continuously. Signal processing, recording and animal care have been described in detail earlier [10]. In 35 dogs, complete AVB had been created by radiofrequency ablation as previously described [14]. Of these, 8 were studied acutely, 20–30 min after AV-nodal ablation, whereas the remaining 27 animals were studied after a minimum of 3 weeks, a sufficient time period for stabilisation of electrical remodelling [14].

2.2. Experimental protocol

Dofetilide was dissolved in 100 μl 0.1 M HCl and diluted in 0.9% saline to a final volume of 0.5 ml/kg bodyweight and administered over 5 min or until TdP appeared. The acute electrophysiological effects of dofetilide were studied for 15 min covering the time-points of both maximal plasma concentration [9] and maximal cardiac effect [10]. Any TdP that degenerated into ventricular fibrillation was stopped by electrical cardioversion.

2.3. Data analysis

Applying a custom-made computer programme (ECG-view, Maastricht University, The Netherlands), we measured the following parameters offline at a resolution of 2 ms: RR and QT intervals from lead II and LV and RV MAP duration to 100% repolarisation (MAPD). All measurements were performed on 30 consecutive beats with the same focus of activation before and 10 min after the start of dofetilide administration. Due to substantial extrasystolic activity of the ventricles in chronic-AVB dogs after dofetilide, analysis was performed immediately prior to the first extrasystolic beat. Interventricular dispersion of repolarisation duration (ΔMAPD) was defined as LV minus RV MAPD. Heart-rate corrected QT intervals were calculated according to van de Water’s formula [15]. BVR was determined according to earlier publications [5]. Briefly, Poincaré plots were drawn from 30 consecutive LV MAPD measurements and short-term variability (STV_{LV} = \sum D_n - D_{n-1}/(30 \times \sqrt{2}), where D_n represents the LV MAPD of the nth beat), representing the mean orthogonal distance to the line-of-identity, was calculated. Additionally, STV of the RR, PP, and QT intervals (STV_{RR}, STV_{PP}, and STV_{QT} respectively) was determined using the same algorithm.

Torsades de pointes was defined as a polymorphic ventricular tachycardia of at least 5 beats with a typical twisting around the isoelectric line in the setting of a prolonged QT interval. A dog was considered inducible when 3 or more TdP occurred as a consequence of dofetilide administration. A second investigator confirmed all observations and measurements.

2.4. Statistical analysis

Pooled data are expressed as mean±SD. All comparisons of electrophysiological data were performed with a one- or two-way ANOVA followed by a Bonferroni t-test when appropriate. Inducibility was compared using Fisher’s
Exact Test. Association between pairs of variables was analysed with Pearson product moment correlation test. SigmaStat (v. 2.03; SPSS Inc.) was used for statistical analysis. Significance was set at \( P<0.05 \). The area under the receiver-operating characteristics was used to assess the proarrhythmic-predictive power of electrophysiological values. Furthermore, we determined the predictive power of electrophysiological parameters combined through multiplication \((A \times B, \text{where } A \text{ and } B \text{ are 2 different electrophysiological parameters})\).

### 3. Results

#### 3.1. Electrophysiological parameters defining the 3 groups

As expected, the sinus rhythm group was characterised by a faster ventricular rate than the AVB groups (Table 1). In contrast, the shortest PP intervals were seen in the acute-AVB dogs. Although repolarisation duration in general showed a trend towards prolongation after AVB, this was entirely due to the slowed ventricular rate, as the QTc intervals were equal at sinus rhythm and acute AVB. Electrical remodelling after AVB quantified as QTc prolongation relative to sinus rhythm was 2 ± 3 ms (1%; \( P=\text{NS}; n=8 \)) and 95 ± 49 ms (34%; \( P<0.05; n=27 \)) for acute and chronic AVB, respectively. Prolonged repolarisation times at chronic AVB were also observed in the group comparison of Table 1. Representative examples of the electrophysiological parameters are given in Fig. 1.

The dofetilide challenge prolonged the RR and QT intervals as well as LV and RV MAPD in all 3 groups (Table 1). The absolute increase in ventricular repolarisation duration was comparable between the 3 groups (Table 1), although maximum values were higher in chronic-AVB dogs. Torsades de pointes arrhythmia was neither observed at baseline nor after dofetilide in dogs in sinus rhythm or in acute AVB (Fig. 1), whereas the incidence of dofetilide-induced TdP in the chronic-AVB group was 74%.

#### 3.2. Parameters of temporal dispersion in the 3 groups

Short-term variability of the LV MAPD increased as a consequence of remodelling after AVB, whereas bradycardia alone did not alter STVLV (Fig. 2A). Variability of the beat-to-beat cycle length (STVRR) during idioventricular rhythm was larger than when the RR interval was measured during sinus rhythm, but it was not affected by ventricular remodelling. Dofetilide caused an increase in the STVRLV only in the remodelled chronic-AVB dogs and not in the other 2 groups. STVRR was only affected by dofetilide when the ventricles were under sinus-node control (Fig. 2A).

In sinus rhythm, the dofetilide-induced increase in STVRR (1.3 ± 0.8 to 2.9 ± 1.7 ms; \( P<0.05; \) Fig. 2), had no effect on STVR (1.0 ± 0.2 to 1.2 ± 0.4 ms; \( P=\text{NS} \)) or STVRLV (0.7 ± 0.1 to 0.7 ± 0.1 ms; \( P=\text{NS} \); Fig. 2A). Representative examples of Poincaré plots are shown in Fig. 3. Even when performing a beat-to-beat heart-rate correction of the QT interval, the STV of these QTc intervals was not increased (STVQTc: 1.1 ± 0.3 to 1.3 ± 0.4 ms; \( P=\text{NS} \)).

STVP was comparable to STVRR in sinus rhythm and increased with dofetilide (STVP: 2.0 ± 0.9 to 3.4 ± 1.9 ms; \( P<0.05; n=12 \)). To evaluate the effect of ventricular bradycardia and remodelling on the atria, we determined STVP, which increased to 12.0 ± 18 ms (\( P<0.05; n=27 \)) after 3-week AVB. This increase was based on a heterogeneous response, as evidenced by a range of STVP between 1.5 and 71 ms (Fig. 4). Dofetilide did not significantly affect STVP after AVB (7.6 ± 7.8 and 17.5 ± 15 ms after acute and chronic AVB, respectively; \( P=\text{NS} \) for both).

#### 3.3. Electrophysiological characteristics of the TdP-prone dog

Seven of the 27 dogs with chronic AVB were resistant to dofetilide-induced TdP. Compared to the inducible chronic-AVB dogs, RR and QT intervals, LV and RV MAPD and STVRLV were all significantly lower at baseline in the resistant dogs (Table 2). Dofetilide increased most electrophysiological parameters in both sub-groups, and both RR and QT intervals reached higher maximal values in the inducible sub-group. STVR or STVP was not affected by dofetilide, however STVRLV was only increased in the TdP-inducible dogs (Table 2; Fig. 5).

The TdP-predictive value of the different electrophysiological parameters was determined from the chronic-AVB dogs (Table 3). This analysis was performed by calculating

### Table 1

Electrophysiological parameters before and after administration of 25 μg/kg dofetilide in the 3 groups of dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sinus rhythm</th>
<th>Acute AVB</th>
<th>Chronic AVB</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>524±83</td>
<td>1111±281</td>
<td>1245±179</td>
</tr>
<tr>
<td>PP</td>
<td>524±83</td>
<td>372±31</td>
<td>558±105</td>
</tr>
<tr>
<td>QT</td>
<td>246±24</td>
<td>303±34</td>
<td>397±54†</td>
</tr>
<tr>
<td>QTc</td>
<td>288±18</td>
<td>293±38</td>
<td>376±46</td>
</tr>
<tr>
<td>LV MAPD</td>
<td>206±15</td>
<td>239±22</td>
<td>337±41</td>
</tr>
<tr>
<td>RV MAPD</td>
<td>191±15</td>
<td>224±21</td>
<td>295±39</td>
</tr>
<tr>
<td>ΔMAPD</td>
<td>16±11</td>
<td>14±8</td>
<td>42±27</td>
</tr>
<tr>
<td>TdP incidence</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

All values in milliseconds unless otherwise noted. TdP inducibility is quantified relative to group sizes (12, 8 and 27, respectively). *, \( P<0.05 \) versus sinus rhythm; †, \( P<0.05 \) versus acute AVB; ‡, \( P<0.05 \) versus baseline.
the area under the curve of the receiver-operating characteristics (Fig. 6). This area for STV_LV after dofetilide administration was 1.0 indicating total separation of STV_LV values. As illustrated in Fig. 6, all TdP-inducible chronic-AVB dogs had an acute dofetilide-induced elevated STV_LV reaching values above 3.0 ms. On the other hand, all resistant dogs had values below 3.0 ms. A combination of 2 of the electrophysiological parameters by simple multiplication increased the area under the curve considerably in several incidences (Table 4).

4. Discussion

With the present study we confirm that baseline STV_LV is persistently increased in chronic-AVB dogs with remodelled hearts, when compared to dogs in acute AVB. The novel findings are that the increased STV_LV is a result of ventricular remodelling and independent of heart rate or STV_RR. Secondly, STV_RR is significantly increased immediately after AVB, which persists over weeks during cardiac remodelling, whereas STV_PP is only elevated secondary to...
the ventricular remodelling. This is the first study to document that $I_{Kr}$ block causes comparable QTc prolongation across a range of cardiac pathologies from healthy to compensated hypertrophy, whereas STVLV is transiently increased only in the individual that later develops TdP.

4.1. Cardiac ventricular remodelling and BVR

Volume-overload induced cardiac remodelling after AVB has been a subject of intense interest over the years. Next to the structural and functional remodelling processes in dogs, a profound electrical remodelling takes place, contributing to the increased proarrhythmic phenotype present after 3 weeks of AVB. Table 1 shows that the AV-nodal ablation causes bradycardia, whereas the repolarisation-dependent parameters are not altered at this acute stage, especially when corrected for heart rate. Earlier studies have shown that cardiac output is momentarily decreased at this point despite an adrenergically induced increase in stroke volume [16,17]. Over weeks, cardiac output is restored as biventricular eccentric hypertrophy develops to facilitate an increase in stroke volume and the adrenergic drive levels off [14,17,18]. At this point, electrical remodelling has prolonged the ventricular repolarisation partly through a downregulation of $I_{Kr}$ and

Fig. 2. (A) Temporal variability of ventricular repolarisation and rate at baseline (open bars) and after administration of 25 $\mu$g/kg dofetilide i.v. (gray bars) in anaesthetised dogs in sinus rhythm, acute (AAVB) and chronic (CAVB) AVB. At baseline, STVLV is increased in the chronic-AVB group, and dofetilide only elevates STVLV in this group. *, P<0.05. Ventricular-rate variability quantified by STVRR is increased after AV-node ablation, but this is not remodelling dependent. Dofetilide increases the sinus rhythm STVRR, but has no effect on STVRR after AVB. Actual values are noted within bars. Panel (B) shows STVLV as a function of RR interval and STVRR for individual dogs. There was a statistical significant correlation between the RR interval and STVLV ($r=0.6; P<0.05; n=94$; left), but not between STVRR and STVLV ($r=0.1; P=NS; n=94$; right).

Fig. 3. Four pairs of representative Poincaré plots of the RR, QT, and QTc intervals and LV MAPD for the same 30 consecutive beats in sinus rhythm. Open arrow, baseline; closed arrow, dofetilide. Only the variability of the RR interval is increased by dofetilide, whereas the QT, QTc, and LV MAPD plots are virtually unchanged.
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I_{Ks}, an upregulation of the sodium–calcium exchange current, and increased calcium release from the sarcoplasmic reticulum [11,19]. The results of the present study strongly suggest that increased BVR is another hallmark of ventricular electrical remodelling. Together, the remodelling processes render the dogs with chronic AVB susceptible to drug-induced and spontaneous TdP arrhythmias [9,10,13,14,16,20]. In Table 1, we confirm our earlier results that the repolarisation-dependent parameters like QT, QTc, LV and RV MAPD alongside interventricular dispersion of repolarisation duration are all increased at chronic AVB. Fig. 2A shows that BVR is independent of the acute bradycardia and only increases as a consequence of ventricular remodelling, like the other repolarisation parameters in Table 1. Interestingly, beat-to-beat variability of the ventricular rate (STVRR) is significantly increased after AVB but does not alter further during remodelling to chronic AVB. Thus, the present study shows for the first time that the increased STV_{LV} seen at chronic AVB is a consequence of the remodelling processes rather than directly induced by a decreased ventricular rate, whereas an increased STV_{RR} is intrinsic of the idioventricular rate and not affected by cardiac remodelling (Fig. 2A). Furthermore, this implies that bradycardia does not contribute to BVR in non-remodelled circumstances.

4.2. Drug-induced TdP in chronic-AVB dogs

Administration of QT-prolonging drugs causes a significant increase in STV_{LV} prior to the occurrence of TdP (Fig. 5), as have been shown previously [5,20,21]. Furthermore, QT-prolonging agents free of proarrhythmia in the chronic-AVB dogs do not induce an increase of STV_{LV} [5,20]. The present study was not undertaken to demonstrate the proarhythmic properties of dofetilide, which has been identified previously by ourselves and in large clinical trials [10,22]. Rather, we wished to investigate the relationship between various electrophysiological parameters, including BVR, and individual susceptibility to drug-induced TdP.

The theory of multiple hits on repolarisation suggests that several consecutive reductions of repolarisation reserve are required for the initiation of TdP [20,23]. In our setting, the first perturbation of repolarisation is the AV-nodal ablation causing bradycardia. Secondly, weeks of cardiac remodelling sets the stage for TdP. Finally, a combination of anaesthesia and fast intravenous administration of a proarhythmic drug triggers a series of events, including increased BVR, prolonged and increased spatial heterogeneity of repolarisation duration, occurrence of early afterdepolarisations and extrasystoles, often culminating in reproducible TdP arrhythmias.

The difference between resistant and inducible chronic-AVB dogs (Table 2) despite identical hits on repolarisation reserve is likely to be dependent on the genetic background of the dogs, although further investigations into this area are needed before this remains clear. Table 2 shows that resistant dogs have a faster idioventricular rate than TdP-inducible dogs, raising the possibility that these animals experience less electrical remodelling. This could be secondary to different levels of contractile or structural remodelling in the two groups, however these remodelling aspects were not determined in the present study. Nevertheless, cardiac remodelling is essential for the induction of arrhythmia.

4.3. Beat-to-beat variability

By using Poincaré plots, STV is one way of analysing BVR. A dose-dependent TdP occurrence after d-sotalol was tightly associated with the transient increase in STV_{LV}, whereas the absence of TdP after a QT prolonging drug is reflected in an unchanged STV_{LV} [5]. Later, we documented that anti-torsadogenic preventive or interventional treatments are associated with stabilised or even decreased STV_{LV} [20]. In the sinus rhythm dogs, dofetilide increased STV_{PP} and STV_{RR} but had no effect on either STV_{QT} or STV_{LV} (Figs. 2 and 3). Thus, the repolarisation in these dogs is strong enough to compensate for the irregular diastolic intervals and keeping action-potential duration constant. Furthermore, the overall range of RR changes within the 30 beats in a dog is

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Resistant chronic AVB</th>
<th>Inducible chronic AVB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Dofetilide</td>
</tr>
<tr>
<td>RR</td>
<td>1067±182</td>
<td>1175±205</td>
</tr>
<tr>
<td>PP</td>
<td>456±57</td>
<td>493±60</td>
</tr>
<tr>
<td>QT</td>
<td>355±52</td>
<td>422±64†</td>
</tr>
<tr>
<td>QTc</td>
<td>349±40</td>
<td>406±51†</td>
</tr>
<tr>
<td>LV MAPD</td>
<td>297±38</td>
<td>399±67†</td>
</tr>
<tr>
<td>RV MAPD</td>
<td>261±41†</td>
<td>337±72†</td>
</tr>
<tr>
<td>ΔMAPD</td>
<td>37±38</td>
<td>92±54†</td>
</tr>
<tr>
<td>STV_{VR}</td>
<td>6.0±2.5</td>
<td>5.2±1.7</td>
</tr>
<tr>
<td>STV_{PP}</td>
<td>7.6±7.2</td>
<td>12.9±11</td>
</tr>
<tr>
<td>STV_{LV}</td>
<td>1.7±0.4</td>
<td>1.9±0.4</td>
</tr>
</tbody>
</table>

All values in milliseconds. †, P<0.05 versus chronic AVB dogs; *P<0.05 versus baseline.
<10% of the mean RR interval, probably too small to significantly influence action potential duration. Interestingly, the beat-to-beat heart-rate correction did not transfer the dofetilide-induced increase in STVRR to differences in STVQT. Caution should be taken in interpreting these results, as heart-rate correction formulas have not been designed to work on an immediate beat-to-beat basis. Furthermore, changes in repolarisation tend to lag behind the heart-rate change [24,25].

In an awake study using telemetry monitoring of 6 dogs in sinus rhythm, dofetilide (30 μg/kg i.v.) prolonged the QT interval by 15% without significant effect on the heart rate [26]. STVQT calculated over 100 beats did not change significantly (6.5 ± 3.7 versus 10.4 ± 3.9 ms; P = NS) as a consequence of dofetilide administration. Thus, compared to the present study (Table 1), the awake situation shows a shorter QT at baseline and a smaller dofetilide-induced increase in the QT interval, however a larger baseline STVQT. Unfortunately, STVRR was not quantified in the awake study, as a considerable respiration-induced RR interval variability in conscious dogs is known to exist [27], which could contribute to a higher STVQT at baseline. We and others have shown that this dose of dofetilide does not cause TdP arrhythmia in sinus rhythm dogs either with or without anaesthesia [10,26].

Beat-to-beat QT interval measurements in dogs with AVB are hampered by P waves coinciding with the end of the T wave (Fig. 1). When such beats are skipped in the analysis, the direct beat-to-beat consecutiveness is lost and sensitivity declines [5]. Furthermore, we have previously shown that STVRR is a poor predictor of drug-induced TdP [5,13]. In the anaesthetised dogs with AVB, STVLV is thus the preferable measure of repolarisation lability.

The shortened PP interval directly after AVB (Table 1) has been shown earlier [14,17,18] and is generally attributed to the increased adrenergic activity compensating the acute drop in cardiac output. The PP intervals are normalized to pre-AVB levels after 2 weeks of AVB [14,17,18]. Still, long PP intervals seem to be a proarrhythmic risk factor in the chronic-AVB dogs (Table 2), which could indicate that either low adrenergic or high vagal tone contributes to the proarrhythmic trigger. A high adrenergic tone, suggested by a short PP interval, would theoretically imply a β-adrenoceptor-mediated activation of the partly downregulated Ks, preventing an excessively prolonged and unstable action potential, thereby possibly serving as a safety factor, reducing TdP inducibility. This is probably a delicate balance of the autonomic nervous system, as intense and acute β-adrenergic stimulation is proarrhythmic [28].

Interestingly, the wide range of STVPP values in the dogs with chronic AVB (Fig. 4) indicates different levels of atrial remodelling despite comparable ventricular remodelling after AVB. This could possibly be based on atrial vulnerability to stretch as the atria are regularly contracting against closed valves after complete AVB. The chronic-AVB dogs with the largest STVPP are thus sensitive to atrial stretch induced by ventricular contraction. Further research is needed to quantify and understand this atrial remodelling in detail.

### 4.4. Electrophysiological parameters predicting TdP

Fig. 6 illustrates receiver-operating characteristics (ROC) for RR, QT, and STVLV with and without pharmacological challenge showing the specificity as a function of sensitivity over a large range of cut-off points to avoid the bias of choosing artificial cut-off points. The area under the curve indicates the predictive value of the given parameter, where an area of 1 indicates 100% specificity and 100% sensitivity for at least 1 cut-off point. At baseline, the most powerful predictors of individual susceptibility to TdP are long PP intervals and elevated STVLV (Table 3). By combining 2 electrophysiological parameters through simple multiplication, the predictive power could be increased in many instances (Table 4). At baseline, multiplication of the PP interval and STVLV gives a rather arbitrary value but a high TdP-predictive power. Dofetilide

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Dofetilide</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>0.87</td>
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</tr>
<tr>
<td>PP</td>
<td>0.91</td>
<td>0.92</td>
</tr>
<tr>
<td>QT</td>
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<td>0.90</td>
</tr>
<tr>
<td>QTc</td>
<td>0.74</td>
<td>0.88</td>
</tr>
<tr>
<td>LV MAPD</td>
<td>0.86</td>
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</tr>
<tr>
<td>RV MAPD</td>
<td>0.84</td>
<td>0.71</td>
</tr>
<tr>
<td>ΔMAPD</td>
<td>0.50</td>
<td>0.58</td>
</tr>
<tr>
<td>STVPP</td>
<td>0.71</td>
<td>0.51</td>
</tr>
<tr>
<td>STVLV</td>
<td>0.73</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Area under the receiver-operating characteristic plots (Fig. 6). The closer the area for a given parameter is to 1, the better its proarrhythmic-predictive performance in anaesthetised dogs with chronic AVB. *, Low STVPP is predictive for TdP, whereas high values for all other analysed electrophysiological parameters have proarrhythmic-predictive value. n = 27.
caused a significant increase in STV_{LV} in the TdP-inducible dogs only (Table 2), but more importantly all values of STV_{LV} increased to over 3.0 ms in the group, whereas none of the resistant dogs reached this level. Hence, there is a total separation of the 2 groups by means of STV_{LV} (Fig. 6) and the resulting area under the ROC curve is 1 (Table 3). This finding is further accentuated by the presence of persistently elevated BVR above 3.0 ms in retrospectively analysed chronic-AVB dogs that died suddenly under conscious, drug-free circumstances [13].

In the present study, ΔMAPD represented spatial dispersion of repolarisation duration, whereas temporal dispersion was characterised by BVR. Interventricular dispersion of MAPD may not directly represent the spatial dispersion required for the perpetuation of triggered TdP [29]. Nevertheless, increased ΔMAPD is likely to suggest steeper gradients of spatial repolarisation dispersion that could infringe an early afterdepolarisation-triggered extrasystole. Generally, interventricular dispersion is larger than intraventricular dispersion of

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**Table 4**

Proarrhythmic predictive values of electrophysiological parameters combined by multiplication

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>PP</th>
<th>QT</th>
<th>QTc</th>
<th>LV MAPD</th>
<th>RV MAPD</th>
<th>ΔMAPD</th>
<th>STV_{RR}^{-1}</th>
<th>STV_{PP}</th>
<th>STV_{LV}</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>–</td>
<td>0.95</td>
<td>0.87</td>
<td>0.84</td>
<td>0.92</td>
<td>0.83</td>
<td>0.59</td>
<td>0.79</td>
<td>0.81</td>
<td>0.97</td>
</tr>
<tr>
<td>PP</td>
<td>0.89</td>
<td>–</td>
<td>0.89</td>
<td>0.88</td>
<td>0.94</td>
<td>0.95</td>
<td>0.64</td>
<td>0.79</td>
<td>0.75</td>
<td>0.99</td>
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<tr>
<td>QT</td>
<td>0.89</td>
<td>0.93</td>
<td>–</td>
<td>0.77</td>
<td>0.86</td>
<td>0.91</td>
<td>0.58</td>
<td>0.79</td>
<td>0.76</td>
<td>0.98</td>
</tr>
<tr>
<td>QTc</td>
<td>0.89</td>
<td>0.92</td>
<td>0.89</td>
<td>–</td>
<td>0.85</td>
<td>0.86</td>
<td>0.57</td>
<td>0.78</td>
<td>0.75</td>
<td>0.96</td>
</tr>
<tr>
<td>LV MAPD</td>
<td>0.83</td>
<td>0.91</td>
<td>0.89</td>
<td>0.86</td>
<td>–</td>
<td>0.88</td>
<td>0.59</td>
<td>0.81</td>
<td>0.77</td>
<td>0.96</td>
</tr>
<tr>
<td>RV MAPD</td>
<td>0.79</td>
<td>0.87</td>
<td>0.83</td>
<td>0.81</td>
<td>0.74</td>
<td>–</td>
<td>0.84</td>
<td>0.75</td>
<td>0.75</td>
<td>0.90</td>
</tr>
<tr>
<td>ΔMAPD</td>
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<td>0.52</td>
<td>0.52</td>
<td>0.50</td>
<td>0.52</td>
<td>0.52</td>
<td>–</td>
<td>0.69</td>
<td>0.72</td>
<td>0.59</td>
</tr>
<tr>
<td>STV_{RR}^{-1}</td>
<td>0.68</td>
<td>0.66</td>
<td>0.66</td>
<td>0.64</td>
<td>0.68</td>
<td>0.64</td>
<td>0.55</td>
<td>–</td>
<td>0.59</td>
<td>0.83</td>
</tr>
<tr>
<td>STV_{PP}</td>
<td>0.71</td>
<td>0.70</td>
<td>0.71</td>
<td>0.70</td>
<td>0.71</td>
<td>0.67</td>
<td>0.70</td>
<td>0.64</td>
<td>–</td>
<td>0.81</td>
</tr>
<tr>
<td>STV_{LV}</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.81</td>
<td>0.95</td>
<td>0.90</td>
<td>–</td>
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</table>

Area under the receiver-operating characteristic plots for electrophysiological parameters combined by multiplication. Since low STV_{RR} suggests increased risk of TdP (Table 3), the multiplication algorithm was altered to A × STV_{RR} ^{-1}. Values with grey background are derived from electrophysiological parameters after the administration of dofetilide. n=27.
repolarisation duration [30], however the latter was not assessed in the present study. Discrete ventricular areas with substantial discordant BVR could give rise to moments of significant intraventricular dispersion setting the stage for TdP arrhythmias. Administration of dofetilide to chronic-AVB dogs (Table 2) increases the proarrhythmic substrate (e.g., QT interval and spatial dispersion of repolarisation), whereas triggers (e.g., elevated BVR and extra systoles) are only present in the inducible dogs.

4.5. Limitations

This study limits BVR measurements to anaesthetised dogs, suggesting precaution when extrapolating TdP-predictive values to the clinical setting. Presently, there is no satisfactory cellular explanation for the mechanism underlying BVR. As this was not a serial investigation, the electrophysiological characteristics of a dofetilide-challenge in a chronic-AVB dog cannot be tracked back to the sinus rhythm situation. STVQT after AVB could not be determined as precise measurements occasionally are hampered by P waves (Fig. 1).

4.6. Clinical implications

Identification of the patient susceptible to drug-induced life threatening TdP arrhythmias is difficult, and the list of available drugs prolonging cardiac repolarisation is increasing, especially among non-cardiovascular drugs [31]. In-hospital initiation of therapy is standard for an increasing number of drugs to minimise the risk of TdP-induced cardiac mortality. Novel proarrhythmic parameters may enhance the quality and reduce the costs of the pre-treatment evaluation of the individual patient receiving potentially torsadogenic medication.

Pharmacological pre-screening of patients is not ideal [4], however in the present study, dofetilide was used as a tool to elicit proarrhythmic individuals. Our study suggests that baseline BVR, possibly in combination with other electrophysiological parameters, may contribute to the individual risk stratification of patients. Preliminary results suggest that this may be feasible also in the clinical setting [32].

4.7. Conclusions

Beat-to-beat variability of repolarisation duration quantified by STV_{LV} is persistently increased by ventricular remodelling but not directly by the slower ventricular rate after AVB. Neither RR intervals nor variability of the RR interval influence BVR. Only hearts prone to TdP express a transient increase in BVR upon dofetilide challenge. Thus, BVR may aid the identification of the TdP-susceptible patient before manifest proarrhythmia.

References

[18] de Groot SH, Schoenmakers M, Molenschot MM, Leunissen JD, Wellens HJ, Vos MA. Contractile adaptations preserving cardiac


