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Azimilide and dofetilide produce similar electrophysiological and proarrhythmic effects in a canine model of Torsade de Pointes arrhythmias

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Abstract

Torsade de Pointes arrhythmias are a feared proarrhythmic effect of (antiarrhythmic) drugs. In dogs with chronic complete AV-block bradycardia-induced volume overload leads to electrical remodeling, which includes increased susceptibility to drug-induced Torsade de Pointes arrhythmias. The IKr channel blocker, dofetilide (Tikosyn™, 0.025 mg/kg/5 min), and the less specific ion channel blocker, azimilide (5 mg/kg/5 min), were compared in nine anesthetized dogs at 4 and 6 weeks of AV-block in a randomized cross-over design. Dosages were based on our own dose-dependence studies and on anti-arrhythmic dosages reported in the literature. Monophasic action potential catheters were placed endocardially in both the left and right ventricle to measure action potential duration, visualize early afterdepolarizations, and to assess interventricular dispersion of repolarization (i.e. left ventricular monophasic action potential duration (at 100%) minus right ventricular monophasic action potential duration (at 100%). Cycle length of idioventricular rhythm, QT-time and the occurrence of drug-induced Torsade de Pointes arrhythmias were determined using the surface electrocardiogram (ECG). Before drug administration, the electrophysiological parameters were identical at 4 and 6 weeks. Both azimilide and dofetilide increased monophasic action potential duration, cycle length of idioventricular rhythm, and QT-time. Dissimilar lengthening of left ventricular and right ventricular monophasic action potential duration increased the interventricular dispersion significantly from 55 to 110 ms for both drugs. All dogs had early afterdepolarizations, while, in the majority, ectopic ventricular beats developed (dofetilide 8/9 and azimilide 7/9). Torsade de Pointes arrhythmias incidence was comparable for dofetilide (6/9) and azimilide (5/9). In conclusion, azimilide and dofetilide show similar electrophysiological and proarrhythmic effects in our canine model with a high incidence of Torsade de Pointes arrhythmias.

Keywords: Chronic complete AV-block dog; Electrical remodeling; Class III drugs; QT, acquired long

1. Introduction

The introduction of newer anti-arrhythmic agents has been disappointing. The clinical application of class III drugs, e.g. D-sotalol and dofetilide, did not reduce mortality in patients after myocardial infarction (Torp-Pedersen et al., 1999; Waldo et al., 1996). Proarrhythmic effects such as Torsade de Pointes arrhythmias probably contributed to these findings (Pratt et al., 1998; Torp-Pedersen et al., 1999). Occurrence of Torsade de Pointes arrhythmias has been related to an increased heterogeneity of repolarization (dispersion) which can be located across the ventricular wall and/or between the ventricles (El-Sherif et al., 1996; Hsieh et al., 2000; Shimizu and Antzelevitch, 2000; Surawicz, 1989; Verduyn et al., 1997; Vos et al., 1998). It has been proposed that these transmural or interventricular differences result, at least partly, from differences in relative densities of the K^+ outward currents (Cheng et al., 1999; Liu and Antzelevitch, 1995; Viswanathan et al., 1999; Volders et al., 1999). These intrinsic differences in action potential duration can become more pronounced during bradycardia, class III drug administration and/or under pathological conditions such as hypertrophy and heart failure (Antzelevitch et al., 1999; Beuckelmann et al., 1993; Cheng et al., 1999; Hsieh et al., 2000; Vos et al., 1998). The only drug which has been reported to decrease dispersion along with a low incidence

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of clinical Torsade de Pointes arrhythmias is amiodarone, a drug with multiple actions (Connolly, 1999; Drouin et al., 1998; Kodama et al., 1999; Merot et al., 1999; Sicouri et al., 1997).

Therefore, early screening for proarrhythmogenic properties of drugs in well characterized animal models becomes mandatory. The dog with chronic complete AV-block shows a high incidence of acquired Torsade de Pointes arrhythmias, caused by a number of adaptive processes including electrical remodeling, and has proven to be a suitable model to screen anti-arrhythmic drugs (Verduyn et al., 1997; Vos et al., 1998).

Many new anti-arrhythmic drugs blocking specifically the delayed rectifier channel IKr, have been related to the occurrence of Torsade de Pointes arrhythmias (Torp-Pedersen et al., 1999; Waldo et al., 1996; Wiesfeld et al., 1992). It has been speculated that drugs which target multiple channels increase the action potential more homogeneously thereby reducing the risk of Torsade de Pointes arrhythmias (e.g. amiodarone) (Connolly, 1999; Hondeghem, 2000).

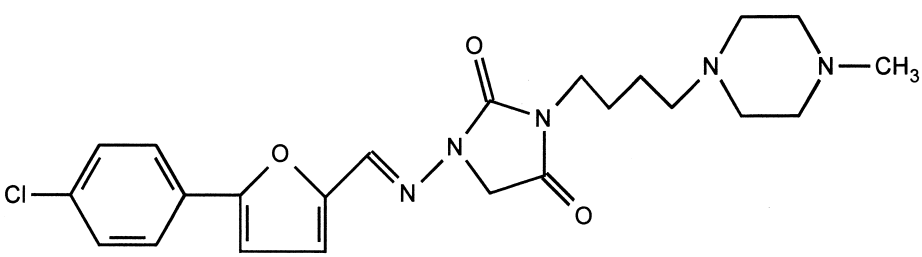
Azimilide (Fig. 1) is a channel blocker of both IKr, IKs, ICa-L and INa (Fermini et al., 1995; Yao and Tseng, 1997), and as such could be expected to prolong action potential duration more homogeneously than selective IKr channel blockers. Thus, we investigated whether azimilide had distinct (proarrhythmic) actions in the electrically remodeled chronic complete AV-block heart in comparison to the specific IKr channel blocker, dofetilide.

2. Methods

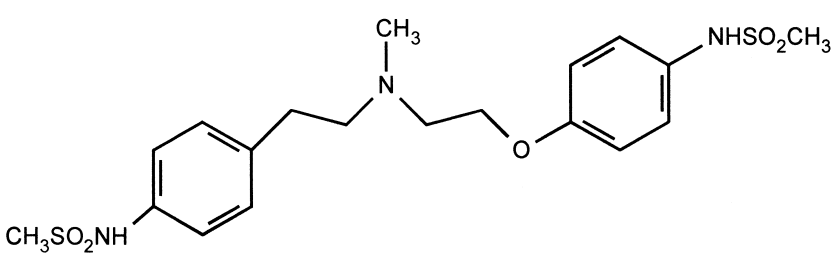
Animal handling was in accordance with the 'Dutch Law on Animal Experimentation (WOD)' and the 'European Directive for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (European Union Directive #86/609/CEE)'. The experiments were approved by 'The Committee for Experiments on Animals (DEC)' of Maastricht University, The Netherlands.

2.1. General

A total of 47 experiments in 20 anesthetized mongrel dogs were performed under aseptic conditions. All animals were studied during sinus rhythm while a subset of 12 dogs was subjected to AV-block as described below. After overnight fasting, anesthesia was induced by (1) premedication i.m. (1 ml/5 kg: 10 mg oxycodon HCl, 1 mg acepromazine, and 0.5 mg atropine sulphate) and (2) sodium pentobarbital i.v. (20 mg/kg, Nembutal, Sanofi). The dogs were artificially ventilated (Dräger, Lubeck, Germany) through a cuffed endotracheal tube at a respiratory rate of 12–14 min using a mixture of oxygen, nitrous oxide (40/60%) and halothane (vapour concentration 0.5–1%). Tidal volume was adjusted (10–15 ml/kg) to maintain the end-expired carbon dioxide concentration between 3.5% and 4%.



Azimilide



Dofetilide

Fig. 1. Chemical formula of azimilide and that of the specific IKr channel blocker, dofetilide.

A thermal mattress was used to maintain body temperature. During the experiment, the dog received 0.5–1 l 0.9% NaCl through the cephalic or saphenous vein to prevent volume depletion. This line was also used to administer drugs.

Proper care was taken before and after the experiments, including use of antibiotics (1000 mg ampicillin) and analgesics (0.015 mg/kg i.m. buprenorfine).

Six surface electrocardiographic leads and two endocardial monophasic action potentials were recorded simultaneously and stored on hard disk. Franz monophasic action potential catheters (EP Technologies, Sunnyvale, CA, USA) were placed endocardially, under fluoroscopic guidance, in the left and right ventricular cavity. The signals were amplified with a customized isolated DC-coupled differential amplifier at a frequency range of 0–500 Hz with a 20-mV calibration pulse. The offset of the amplifier is variable and can be adjusted to the recorded signal. Monophasic action potential phases were defined according to the definitions used for transmembrane potentials (Vos et al., 2000b), where amplitude has been defined as the voltage difference between phases 2 and 4 of the monophasic action potential signal. Besides a minimal amplitude of 15 mV, the monophasic action potential has to have a stable configuration and a smooth shape to be acceptable for measurements.

The ventricular effective refractory period was determined incrementally at twice diastolic threshold by giving an extra stimulus in steps of 5 ms during steady state pacing from the right ventricular monophasic action potential at a cycle length of 350 ms.

2.2. Drug dosages

Azimilide and dofetilide were provided by Procter & Gamble Pharmaceuticals, USA. Azimilide was dissolved in a phosphate buffer solution, while dofetilide was diluted in a 0.9% NaCl water solution. All dosages were given in 5 min.

To select the appropriate drug dosage, we searched initially for the reported anti-arrhythmic efficacy, defined as $\pm 50\%$ prevention or termination against atrial fibrillation or pacing-induced ventricular tachycardia after myocardial infarction in canine arrhythmia models (Black et al., 1993; Drexler et al., 1996; Nattel et al., 1998; Zuanetti and Corr, 1991). The dosages selected (0.05 mg/kg dofetilide ($n = 8$) and 10 mg/kg azimilide ($n = 8$)) increased QTc by 24% and 27%, respectively. This QTc lengthening exceeds our desired range of QTc increase of $15 \pm 5\%$ which is based on the fact that most class III drugs have different sensitivities for atrial versus ventricular tissue, the atrial effective anti-arrhythmic dose being lower than the ventricular one (Baskin and Lynch, 1998). As atrial fibrillation will often be the clinical arrhythmia to treat, screening for Torsade de Pointes arrhythmias should be based primarily on atrial effectiveness. For that reason, the dosages were adjusted to 0.025 mg/kg for dofetilide and to 5 mg/kg for azimilide and retested in two groups of six dogs, eight of which also participated in the first determination (see Results). The latter dosages increased QTc by 13% for azimilide and 19% for dofetilide.

2.3. Torsade de Pointes experiments in chronic AV-block dogs

Twelve of the above dogs were subjected to the creation of AV-block by radio-frequency ablation (Rodriguez et al., 1998). One dog died during the AV-block procedure and one during the first week after the procedure. An endocardial lead (StimTine 1SP 13B 8F; Vitatron Medical, Dieren, The Netherlands) was positioned in the apex of the right ventricle via the external jugular vein.

After the AV-block operation, the animals temporarily received a pacemaker for 24 h. The heart was paced from the right ventricle lead at about 50–60 beats/min and the pacemaker was placed externally in a purpose-designed jacket around the thorax.

To confirm persistence of chronic complete AV-block, surface electrocardiograms (ECGs) were recorded every week. After 4 weeks of chronic complete AV-block, the dogs reach a steady state in their different remodeling processes (Verduyn et al., 1999). Therefore, Torsade de Pointes arrhythmia screening was started after 4 weeks in the remaining 10 dogs, in a random crossover design in which the experiments were performed > 1 week apart. Five dogs received azimilide (5 mg/kg) in the first experiment. If Torsade de Pointes arrhythmias occurred during the drug administration, the infusion was stopped.

2.4. Data analysis

Applying a custom-made computer program (ECG View), with a resolution of 2 ms and adjustable gain and time scale, we measured the following parameters off line: RR interval length, QT-time in lead II, the duration of the monophasic action potential of the left and right ventricle at 100% of repolarization. From these measurements, the interventricular dispersion of repolarization was calculated, defined as left ventricular monophasic action potential duration at 100% minus right ventricular monophasic action potential duration at 100%. Corrected QT-time was calculated using the Bazett formula (Bazett, 1920). All the electrophysiological measurements given were performed at the "maximal" effect of the drug. To determine this moment of maximal effect, we tested the temporal electropharmacological behavior of four dogs in each group.

Monophasic action potentials were also recorded to visualize early afterdepolarizations, which were defined as an interruption of the smooth contour of phase 2 and/or phase 3 of the action potential duration in either monophasic action potential (Vos et al., 2000b). The occurrence of (triggered) ventricular ectopic beats and spontaneous Tor-

Table 1
Comparison of dofetilide (0.025 mg/kg) and azimilide (5 mg/kg) in sinus rhythm dogs ($n = 6$)

	Control	Dofetilide	%
RR	525 ± 130	675 ± 155[a]	29
QT	235 ± 30	315 ± 45[a]	35
QTc	325 ± 15	385 ± 30[a]	19
LV MAPD	205 ± 15	295 ± 50[a]	43
RV MAPD	190 ± 15	260 ± 35[a]	37
ΔMAPD	15 ± 5	35 ± 20	125
VERP	160 ± 15	200 ± 25[a]	26
	Control	Azimilide	%
RR	505 ± 75	625 ± 110[a]	24
QT	245 ± 25	310 ± 35[a]	26
QTc	345 ± 20	390 ± 15[a]	13
LV MAPD	215 ± 25	275 ± 50[a]	27
RV MAPD	200 ± 25	235 ± 35[a]	19
ΔMAPD	15 ± 5	40 ± 20[a]	140
VERP	180 ± 20	200 ± 20[a]	11

Values in ms and means ± S.D.
LV/RV: Left/right ventricular.
MAPD: Monophasic action potential duration.
ΔMAPD: Interventricular dispersion.
VERP: Ventricular effective refractory period.
[a] $P < 0.05$.

sade de Pointes arrhythmias was monitored before and after drug administration. Torsade de Pointes arrhythmias were defined as a polymorphic ventricular tachycardia of at least five beats, characterized by an onset with abnormal QT-prolongation and/or abnormal TU complexes, the electrocardiographic configuration of a progressively changing ventricular axis and spontaneous termination with the exception of rare degeneration into ventricular fibrillation (Eckardt et al., 1998). A dog was defined to be inducible for Torsade de Pointes arrhythmias when such an arrhythmia occurred ≥ 3 times spontaneously. In the case of ventricular fibrillation, cardioversion was applied through patches on the thorax that had been placed in advance.

2.5. Statistics

Pooled data are expressed as means ± standard deviation. Intergroup comparisons of the dosage determination were performed with unpaired Student's *t*-test, whereas serial comparisons in the chronic complete AV-block experiments were performed with paired Student's *t*-test. The time-dependence study statistical analyses were done with a Friedman two-way analysis of variance (ANOVA) with a post-hoc Bonferroni *t*-test. Values of $P < 0.05$ were considered significant.

3. Results

3.1. Electrophysiological effects of azimilide and dofetilide in anesthetized dogs during normally conducted sinus rhythm

The baseline electrophysiological parameters were similar in the two sinus rhythm groups (control, left part of Table 1). The time-dependent effects of dofetilide and azimilide on QT-time can be seen in Fig. 2: the maximum QT-time effect was reached 10 min after the start of the infusion. Therefore, we chose to report all the electrophysiological values for this moment ($t = 10'$, Table 1).

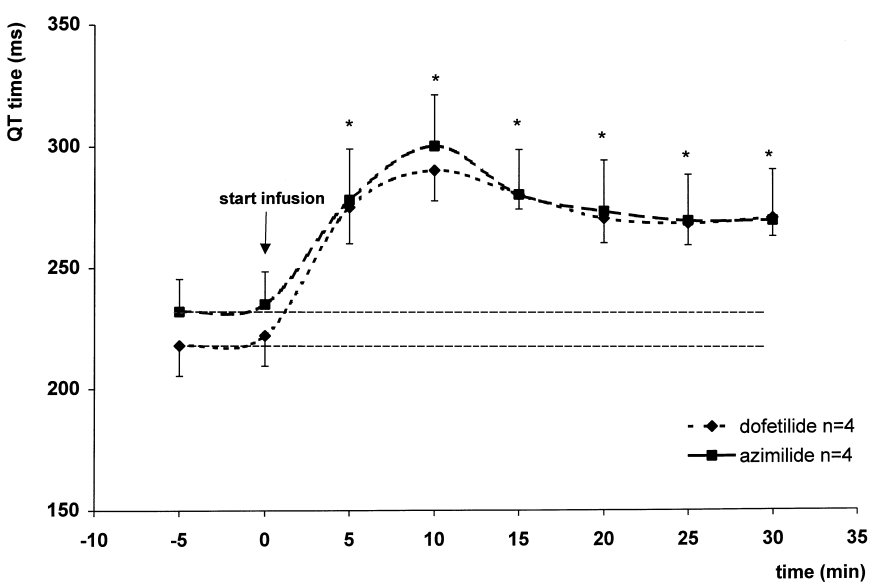


Fig. 2. Time dependence of QT-time changes following azimilide (5 mg/kg/5 min) and dofetilide (0.025 mg/kg/5 min) during sinus rhythm. The drugs act very similarly to prolong repolarization time. The maximum QT effect was reached 10 min after the start of the infusion. After this time, there was a small decline to still significantly elevated values that remained stable over the observation period of 30 min. * $P < 0.05$ vs. $t = 0$ (ANOVA).

Both dofetilide and azimilide caused a significant increase in RR interval, QT(c) duration, left ventricular monophasic action potential duration, right ventricular monophasic action potential duration and ventricular effective refractory period (Table 1). As a result of the more pronounced effect on the left ventricular monophasic action potential duration compared to the right ventricular monophasic action potential duration, the interventricular dispersion doubled after both drugs, but became significant only for azimilide (from 15 ± 5 to 40 ± 20 ms, $P < 0.05$, Table 1). A representative example of the electrophysiological effects of azimilide is given in Fig. 3, panels 1 and 2.

When the two drugs are compared, it appears that at the dosages used, dofetilide is somewhat more potent than azimilide: e.g. dofetilide increased QTc-time by 19% while azimilide produced a 13% increase. During sinus rhythm no arrhythmogenic activity was seen during or after infusion of the drugs.

3.2. Electrophysiological and arrhythmic effects of azimilide and dofetilide at chronic complete AV-block

Of the 10 anesthetized dogs tested initially at chronic complete AV-block 4 weeks, one animal showed arrhythmias prior to drug administration and was therefore excluded from this study.

In Fig. 3, we show the electrophysiological adaptations (electrical remodeling) caused by chronic complete AV-block (panel 1 sinus rhythm versus panel 3 chronic complete AV-block at baseline).

As expected, the baseline values for the dogs tested, serially at chronic complete AV-block, were similar (Table

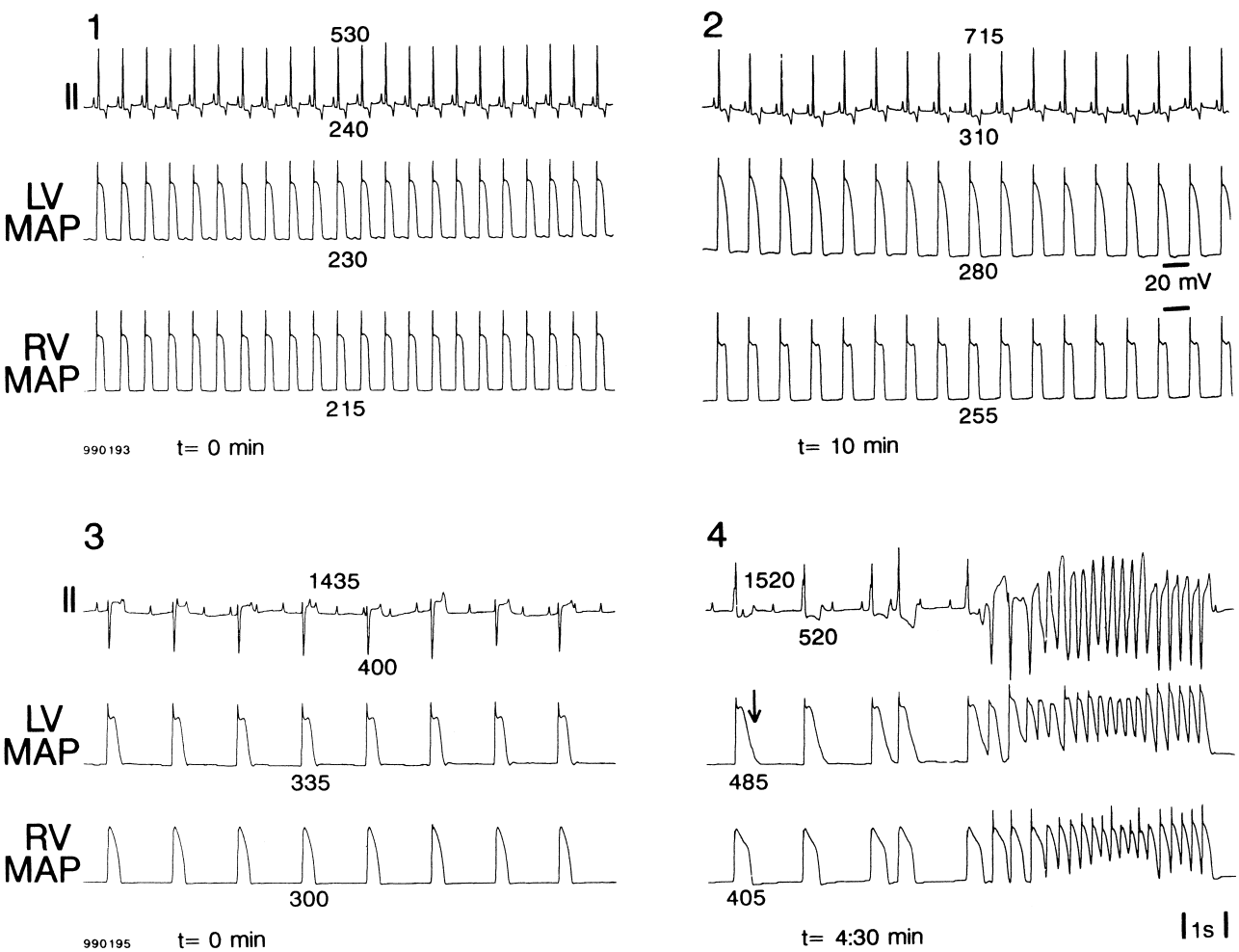


Fig. 3. Effect of azimilide (5 mg/kg/5 min) during sinus rhythm and chronic complete AV-block in the same dog. In all panels, lead II of the surface ECG and two monophasic action potential catheters (MAP) in both the left ventricle (LV) and right ventricle (RV) are shown at a paper speed of 10 mm/s. In panel 1, the baseline situation during sinus rhythm is shown: the interventricular dispersion is minimal (15 ms). Ten minutes after azimilide administration, RR as well as QT-time, LV MAP duration, RV MAP duration, and the interventricular dispersion have all increased (panel 2). At 4 weeks of chronic AV block, bradycardia is clearly visible and accompanied by an increased QT-time, LV and RV MAP duration. The interventricular dispersion is 35 ms (panel 3). After azimilide, RR and QT-time increase further, LV MAP duration increases more than the RV MAP duration leading to a considerable interventricular dispersion of 80 ms. A short–long–short sequence of ventricular ectopic beats initiates a Torsade de Pointes arrhythmia which in this case terminated spontaneously.

Table 2
Comparison of dofetilide (0.025 mg/kg) and azimilide (5 mg/kg) in CAVB dogs ($n = 9$)

	Control	Dofetilide	%
RR	1360 ± 315	1575 ± 375[a]	17
QT	405 ± 65	505 ± 95[a]	25
QTc	350 ± 60	405 ± 70[a]	17
LV MAPD	365 ± 60	490 ± 90[a]	34
RV MAPD	310 ± 45	380 ± 80[a]	23
ΔMAPD	55 ± 25	110 ± 25[a]	100

	Control	Azimilide	%
RR	1420 ± 225	1575 ± 290[a]	11
QT	400 ± 65	500 ± 85[a]	26
QTc	335 ± 50	400 ± 55[a]	19
LV MAPD	370 ± 80	500 ± 110[a]	36
RV MAPD	315 ± 65	390 ± 85[a]	22
ΔMAPD	55 ± 25	110 ± 50[a]	100

Values in ms and means ± S.D.
LV/RV: Left/right ventricular.
MAPD: Monophasic action potential duration.
ΔMAPD: Interventricular dispersion.
[a] $P < 0.05$.

2, left panel). Before drug administration, no arrhythmic activity (early afterdepolarizations or ventricular ectopic activity) was observed. Because Torsade de Pointes arrhythmias often occurred before the end of the dose regimen, we decided to determine all electrophysiological parameters immediately before the Torsade de Pointes arrhythmia (mean: 180 ± 60 s). For those dogs not showing Torsade de Pointes arrhythmias, the measurements were taken at a similar time ($t = 3'$, Table 2).

Dofetilide and azimilide prolonged all repolarization parameters equally, including the interventricular dispersion (Fig. 3, panels 3 and 4 and Table 2). After either drug, early afterdepolarizations developed in all experiments, while in the majority of dogs, single and multiple ventricular ectopic beats occurred (Fig. 3): 8/9 for dofetilide and 7/9 for azimilide (not significantly different). Interaction of this ectopic activity, often in the short–long–short sequence (Fig. 3), along with the considerable interventricular dispersion (e.g. 110 ± 50 ms with azimilide, Table 2 and Fig. 4) evoked Torsade de Pointes arrhythmias reproducibly (Fig. 5). Torsade de Pointes arrhythmia incidence was not different for the two drugs and occurred in 6/9 dogs after dofetilide and in 5/9 dogs after azimilide (Figs. 3–5).

When we compare the electropharmacological response to azimilide at sinus rhythm versus chronic complete AV-block, the interventricular dispersion increased from 15 ± 5

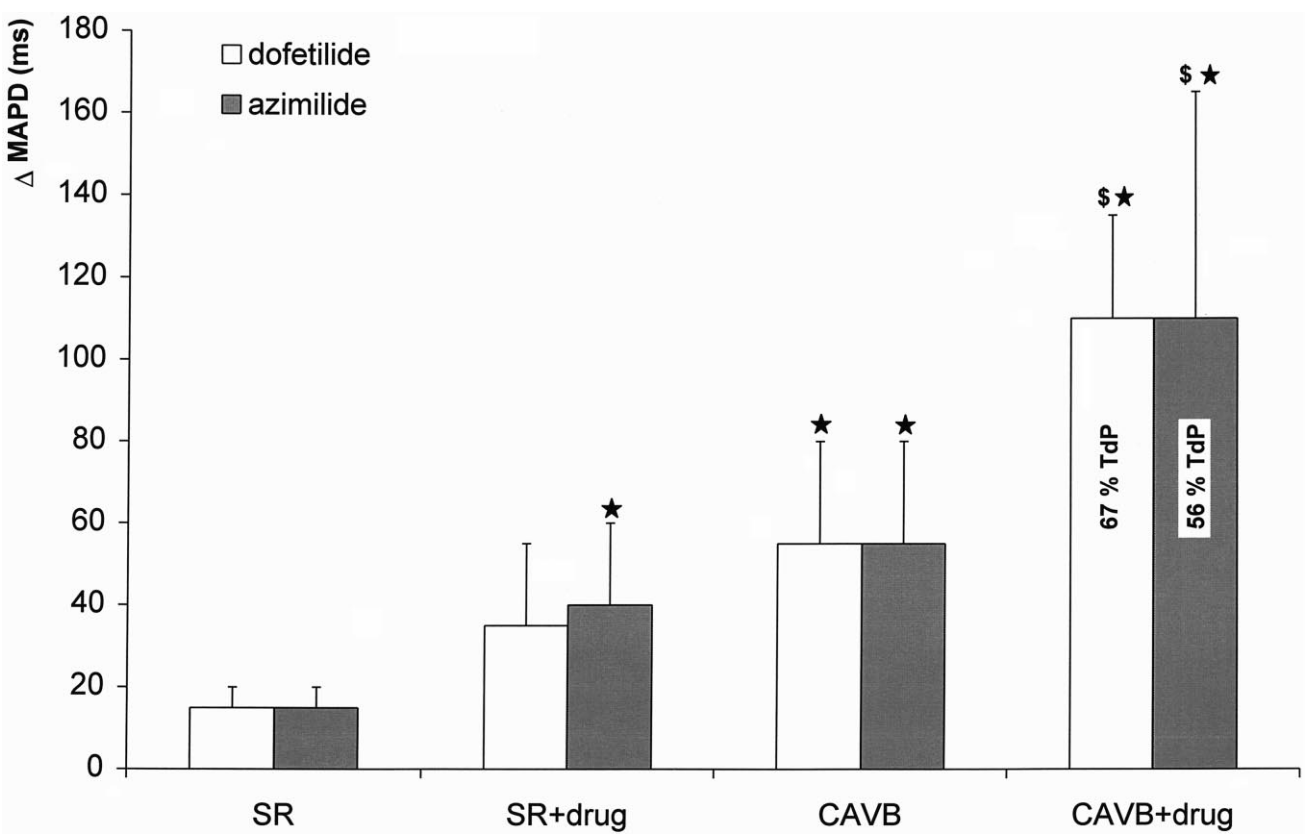


Fig. 4. The changes in interventricular dispersion (ΔMAPD on *Y*-axis) are illustrated under four different circumstances for both drugs. During sinus rhythm (SR) the ΔMAPD was minimal and increased after drug administration. At chronic complete AV-block (CAVB), the ΔMAPD had increased to about 50 ms and showed a further marked increase after drug administration. A similar Torsade de Pointes arrhythmia (TdP) incidence for both drugs was seen. ★, $P < 0.05$ vs. sinus rhythm and $, $P < 0.05$ vs. CAVB.

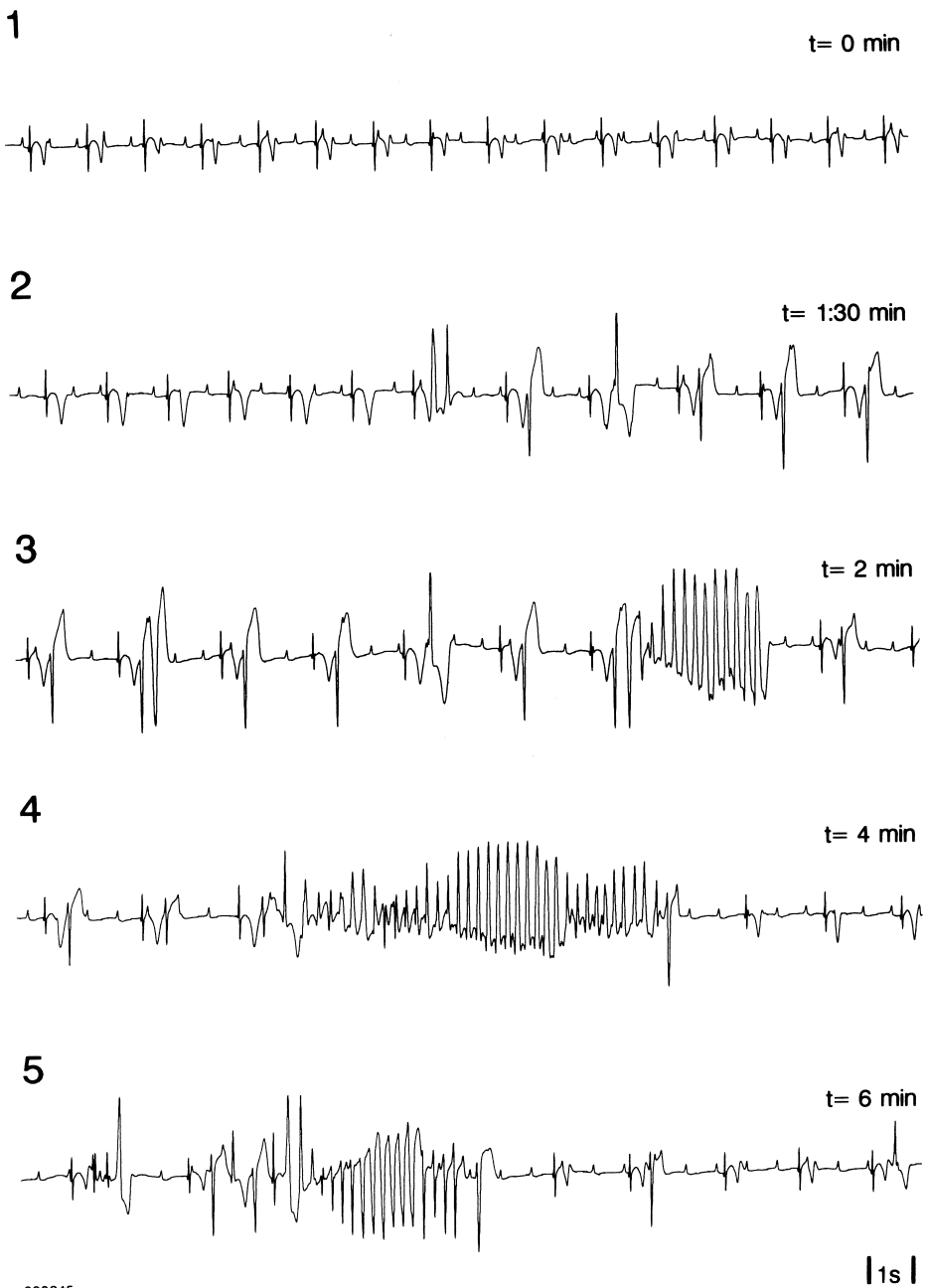


Fig. 5. Reproducible Torsade de Pointes arrhythmias with azimilide (5 mg/kg/5 min) during chronic complete AV-block. A five-panel figure of lead II at a paper speed of 10 mm/s demonstrates the events after administration (in minutes) of azimilide in the chronic AV-block dog. Panel 1 shows the control situation. As early as 1 min 30 sec. after the start of azimilide administration, ventricular ectopic activity developed (panel 2) which was followed by the reproducible initiation of life-threatening Torsade de Pointes arrhythmias, all terminating spontaneously (panels 3 to 5).

to 40 ± 20 ms during normal sinus rhythm and from $55 + 25$ to 110 ± 50 ms when the drug was given at chronic complete AV-block (Fig. 4).

4. Discussion

In the present study, we found that 0.025 mg/kg dofetilide and 5 mg/kg azimilide possessed similar ventricular electrophysiological and proarrhythmic effects in anesthetized dogs with chronic complete AV-block.

Dofetilide acts specifically on the cardiac delayed rectifier potassium channel IKr while azimilide has multiple channel blocking properties (IKr, IKs, ICa-L and INa channels) (Fermini et al., 1995; Yao and Tseng, 1997). Dofetilide (Tikosyn™) is approved for clinical use in the USA for conversion of chronic atrial fibrillation and maintenance of normal sinus rhythm while azimilide is still

under clinical investigation (Camm et al., 1998; Grines, 2000).

The Survival With ORal D-sotalol (SWORD) and Danish Investigations of Arrhythmia and Mortality On Dofetilide (DIAMOND) trials, revealed that agents blocking specifically the IKr channel do not reduce overall mortality (Torp-Pedersen et al., 1999; Waldo et al., 1996). These disappointing results can probably be attributed to the increased risk of proarrhythmia, notably Torsade de Pointes arrhythmias. Torsade de Pointes arrhythmias are generally believed to be dependent on a substrate, dispersion in action potential duration, and a trigger, early afterdepolarization dependent triggered activity (Surawicz, 1989; Verduyn et al., 1997). Selective IKr channel blockade is thought to aggravate the dispersion in action potential duration and facilitate the occurrence of early afterdepolarizations (Antzelevitch et al., 1999; Cheng et al., 1999; Verduyn et al., 1997; Viswanathan et al., 1999). These early afterdepolarizations can give rise to triggered ectopic activity, setting the stage for Torsade de Pointes arrhythmias (Volders et al., 2000).

In contrast, a multiple channel blocker like amiodarone increases the action potential duration without causing dispersion of repolarization and is rarely associated with Torsade de Pointes arrhythmias (Connolly, 1999; Drouin et al., 1998; Kodama et al., 1999; Merot et al., 1999; Sicouri et al., 1997). It is suggested that the low incidence of Torsade de Pointes arrhythmias with amiodarone is, at least partly, related to its Ca-L channel blocking properties, which channel is considered to play a major role in early afterdepolarization formation (Starmer et al., 1995; Volders et al., 2000). In favour of this line of thinking is the fact that drugs which block simultaneously the IK channel and Ca-L channel prolong the action potential duration without the occurrence of Torsade de Pointes arrhythmias (Bril et al., 1996; Carlsson et al., 1996).

Azimilide blocks, in addition to the Ca-L channel, the IKs channel (Fermini et al., 1995; Yao and Tseng, 1997). It has been speculated that (additional) IKs channel blockade may have anti-arrhythmic properties during faster heart rates and an enhanced sympathetic tone, when the IKs channel is believed to play an important role in aggravating dispersion of repolarization (Lynch et al., 1999; Schreieck et al., 1997; Viswanathan and Rudy, 2000).

4.1. Chronic complete AV-block dog model

To test for the proarrhythmogenic potential of anti-arrhythmic drugs, the adrenergically stimulated rabbit and various dog Torsade de Pointes arrhythmias preparations have been used as animal models (Antzelevitch et al., 1999; Carlsson et al., 1993; Hsieh et al., 2000). The chronic complete AV-block dog model has been well characterized for its specific structural, contractile and electrical adaptation processes. In short, compensated biventricular hypertrophy occurs in time, which is accompanied by non-homogeneous increases in endocardial monophasic action potential durations, leading to interventricular dispersion of repolarization. Whereas the differences in ventricular monophasic action potential duration are small during sinus rhythm, dispersion increases considerably after chronic complete AV-block (Fig. 4).

Ionically, the increase in monophasic action potential duration can be attributed, at least partly, to a down regulation of the IK current in the model (Volders et al., 1999). IK current down regulation has been implicated in congenital long QT syndromes (Priori et al., 1999) and has been reported for patients with organic heart disease, such as congestive heart failure (Beuckelmann et al., 1993; Marban, 1999). The latter may explain the apparent increased risk of drug-induced Torsade de Pointes arrhythmias among these individuals (Camm et al., 2000; Roden, 2000). As such, the model is very suitable for demonstrating that a drug would produce an adequate lengthening of QT-time without creating dispersion of repolarization.

Several anti-arrhythmic agents have been tested in this model (Verduyn et al., 1997; Vos et al., 1998), showing an increase in interventricular dispersion which was associated with a Torsade de Pointes arrhythmias incidence ranging from 50% to 65%. Because the electrical adaptations have been stabilized after 4 weeks of chronic complete AV-block (Verduyn et al., 1999), drug testing can be performed serially in the same dog, as we have done in this and a previous study (Verduyn et al., 1997).

Both azimilide and dofetilide had pronounced effects on QTc, left ventricular and right ventricular monophasic action potential duration and ventricular effective refractory period (Table 2). The interventricular dispersion (Fig. 4) increased by lengthening the left ventricular monophasic action potential duration more than the right ventricular monophasic action potential duration. Both drugs caused Torsade de Pointes arrhythmias, preceded by single and multiple ventricular ectopic beats, often in the short–long–short sequence. The short–long–short sequence is an important contributor to augmenting the dispersion and initiating Torsade de Pointes arrhythmias, as we recently described (Verduyn et al., 1997; Vos et al., 2000a). The electrophysiological effects of the drugs described in Table 2 can be an underestimate because, in most animals, the infusion was stopped prematurely due to occurrence of Torsade de Pointes arrhythmias.

The results imply that the non-selective ion channel blockade provided by azimilide is not preferable to the use of the selective IKr blocker dofetilide in the chronic complete AV-block dog model. For this finding, several explanations could be offered: (1) the fact that azimilide did not prevent early afterdepolarizations and related ventricular ectopic beats would suggest an insufficient Ca-L channel blockade by the drug, (2) blocking the IKs channel could be beneficial especially during the several episodes of rate switches, ventricular ectopic beats, which occurred after infusion of the drug. However, it is not clear to what

extent azimilide can still favorably block this channel in the chronic complete AV-block dog in which the IKs current is significantly down regulated (Volders et al., 1999), and (3) azimilide blocks the multiple ion channels with different potencies (e.g. IC 50 IKr 0.4 μmol/l and IKs 3 μmol/l) which could imply no, or less, effect on certain ion channels with the present dosage (Fermini et al., 1995; Yao and Tseng, 1997).

To assess the possible beneficial role of less specific ion channel blockers versus specific IKr channel blockers in the chronic complete AV-block dog model, a proven anti-arrhythmic agent with minimal proarrhythmic adverse effects, such as amiodarone, should be tested in order to examine the validity of the model.

4.2. Conclusion

Azimilide and dofetilide at doses which provide similar electrophysiological effects cause a similar high incidence of Torsade de Pointes arrhythmias in atrioventricular blocked dogs with remodeling.

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