Electrophysiological parameters indicative of sudden cardiac death in the dog with chronic complete AV-block


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Abstract

Background: The dog model of chronic complete AV-block (CAVB) demonstrates a considerable incidence of (witnessed) sudden death (16/117 dogs). In this study we tried to: (1) elucidate the mechanisms of sudden death using an ECG telemetry device and (2) identify retrospectively the risk parameters indicative of this arrhythmogenic death. Methods: Between 1994 and 1998, 78 anesthetized dogs underwent an extensive electrophysiological study including: (1) left- (LV) and right ventricular (RV) monophasic action potential (MAP) recordings to assess ΔMAPD (LV APD minus RV APD) and (2) pacing protocols (PES) to induce torsade de points arrhythmias (TdP) at 4–6 weeks CAVB. Eight animals experienced sudden cardiac death (SCD) during the follow-up period (mean 7±3 weeks CAVB). Since the response of the CAVB dog to class III drugs is not uniform we also made comparisons among the SCD group, TdP drug responders and non-responders. For this purpose we selected all animals which (1) received almokalant (n=15, 0.12 mg/kg/5 min) or ibutilide (n=9, 0.025 mg/kg/5 min) as an additional challenge to induce TdP and (2) had a follow-up period of at least 4 weeks. Results: Six out of eight SCD dogs showed inducible TdP at baseline. Two of eight dogs had telemetric ECG surveillance and both revealed polymorphic VT as the cause of SCD. Baseline ΔMAPD of the SCD (90±15 ms) was significantly higher than the non-SCD group (n=70, 60±30 ms). Of the 24 dogs which received class III drugs, 12 belonged to the TdP responder group. ΔMAPD of the TdP responder group (80±15 ms) was similar to the SCD group and significantly higher compared to the non-responder group (n=12, 40±25 ms). QT-time and cycle length of idioventricular rhythm were not different. Conclusion: In the CAVB dog model, SCD is (1) most probably related to TdP while (2) inducible TdP and the measure of ΔMAPD at baseline indicate susceptibility to SCD. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Arrhythmia (mechanisms); Bradycardia; Long QT syndrome; Repolarization; Sudden death; Ventricular arrhythmias

1. Introduction

In Maastricht, the chronic AV-block (CAVB) dog has been studied extensively to understand its enhanced susceptibility to ventricular arrhythmias [1–5]. The bradycardia induced volume overload by acute AV-block initiates rapidly a number of adaptation processes to compensate for the decreased cardiac output and the increased end-diastolic pressure [5]. These remodeling processes are completed within 4 weeks of CAVB and include (1) development of biventricular eccentric hypertrophy, (2) compensated cardiac hemodynamics and (3) heterogeneous prolongation of the ventricular repolarization time, resulting in an increased dispersion of repolarization (i.e. electrical remodeling) [1,2,5]. These adaptations, alone or synergistically, increase the risk of early afterdepolarizations (EAD) — respectively, delayed afterdepolarization-dependent triggered arrhythmias and drug-induced torsade de points arrhythmias (TdP) [1,2,4–10]. Moreover, a number of (witnessed) sudden deaths occur in the cages after 4 weeks of CAVB.

To assess if sudden death could be attributed to ventricular arrhythmias, a two-lead electrocardiogram (ECG) telemetric device was implanted prospectively. As tele-

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metry revealed sudden death to be arrhythmogenic, our large canine database at baseline CA VB was used to identify retrospectively the electrophysiological parameters which could predict susceptibility to sudden cardiac death (SCD).

2. Methods

Between 1994–1998, the CA VB dog (n=117) was investigated to determine (1) the different remodeling processes in relation to ventricular arrhythmias and (2) to compare the ability of different anti-arrhythmic drugs to induce TdP. During this period 16 out of 117 dogs experienced sudden death.

Before discussing the employment of the telemetry device, the definition of sudden cardiac death and the use of our electrophysiological database, the general methodology will be described briefly.

2.1. General 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.

The methods used for induction of anesthesia, creation of AV-block and the electrophysiological studies performed at 4–6 weeks of AV-block are detailed in previous publications [1,5,6,8,9]. In short, anesthesia was induced by premedication and sodium pentobarbital (20–25 mg/kg) and the dogs were ventilated artificially using a mixture of oxygen, nitrous oxide and 0.5% halothane. AV-block was created by injection of formaldehyde in the AV-groove off line. MAP catheters (EP Technologies Inc., CA, USA) were placed endocardially, 70 non-SCD dogs. Since the response of the CA VB dog to class III drugs is not uniform, we also made electrophysiological comparisons at baseline among the SCD subgroups.

Eight of these 78 animals experienced SCD during the follow-up period (SCD group) and were compared to the 70 non-SCD dogs. Since the response of the CA VB dog to class III drugs is not uniform, we also made electrophysiological comparisons at baseline among the SCD group, drug TdP responders and drug non-responders. For this purpose we selected all dogs which as well (1) showed no (inducible) TdP at baseline, (2) received almokalant (0.12 mg/kg/5 min) or ibutilide (Corvert™, 0.025 mg/kg/5 min) as an additional challenge to induce TdP, and (3)
had a follow-up period of at least 4 weeks after the electrophysiological study performed at 4–6 weeks of CAVB. Part of the almokalant-treated dogs have been published previously [9], although the results are now used for a different purpose.

2.4. Data analysis at CAVB baseline

Applying a custom made computer program (ECG View, Maastricht University), with a resolution of 2 ms and adjustable gain and time scale, the following parameters were measured off line: cycle length of idioventricular rhythm (CL-IVR), QT-time, the duration of the monophasic action potential (MAPD) of the LV and RV at 100% of repolarization. From these measurements, the interventricular dispersion (ΔMAPD) was calculated, defined as LV MAPD minus RV MAPD.

Electrophysiological data were measured during a stable CL-IVR after at least 1 h of anesthesia and are the mean of five consecutive beats. Both at baseline and during class III drugs, the electrophysiological measurements were done beat to beat to determine maximum values.

2.5. Statistics

Pooled data are expressed as mean±standard deviation (S.D.). Two group comparisons between the SCD and the non-SCD group were analyzed by unpaired Student’s t-test. Multiple comparisons between the SCD-, drug TdP- responders, and non-responders groups were performed by one-way analysis of variance (ANOVA) test with a post-hoc Bonferroni t-test. Chi-square test was used when the data were presented as a proportion.

3. Results

3.1. Sudden cardiac death group: electrophysiological and arrhythmogenic parameters

Mean time of SCD was 7±3 weeks of CAVB. Gender, age and the amount of cardiac hypertrophy in the SCD dogs (heart/body weight 12.6±1.5 g/kg) was not different from the non-SCD dogs (heart/body weight 11.5±2.4 g/kg). Two of the eight SCD dogs had a telemetric device implanted and revealed a polymorphic ventricular tachycardia as cause of death. As can be seen in Fig. 1, the tachycardia was preceded by an acceleration in heart rate and the occurrence of ventricular ectopic activity. This particular animal also showed a substantial amount of ectopic activity and a self terminating polymorphic ventricular tachycardia in the hours preceding its death. In the other six SCD animals, having no telemetric device, other causes of death could be excluded. Two of these six animals were witnessed to have SCD while excited, dying in front of the animal technician. Resuscitation equipment was not available in the stables.

In Table 1 (left part), it can be seen that CL-IVR, QT-time and RV MAPD did not differ between the SCD dogs and the non-SCD dogs (n=70). LV MAPD and ΔMAPD were however significantly different between the two groups.

When looking at the arrhythmia incidence in the SCD group, six of eight animals (75%) already demonstrated TdP at baseline: in four dogs multiple episodes of spontaneous TdP were seen during the electrophysiological study (Fig. 2) while in five dogs TdP could be induced by PES. In the non-SCD group the incidence of TdP at baseline was 11/70 (16%, P<0.001 SCD vs. non-SCD group).

![sudden cardiac death](https://example.com/sudden-cardiac-death.png)

**Fig. 1.** Example of sudden cardiac death in the CAVB dog, recorded by telemetry in the cage. A two-lead ECG is shown at a paper speed of 10 mm/s. An acceleration of the rhythm with frequent ectopic activity (asterisk) is followed by a polymorphic ventricular tachycardia which degenerated in ventricular fibrillation resulting in sudden cardiac death. The numbers refer to the cycle length of the different beats.
Table 1
Electrophysiological parameters of the non-SCD and SCD group, TdP responders and non-responders*

<table>
<thead>
<tr>
<th></th>
<th>Non-SCD (n=70)</th>
<th>SCD (n=8)</th>
<th>TdP responders (n=12)</th>
<th>Non-responders (n=12)</th>
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<tbody>
<tr>
<td>CL-IVR</td>
<td>1410±315</td>
<td>1620±225</td>
<td>1455±360</td>
<td>1420±360</td>
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<tr>
<td>QT-time</td>
<td>395±65</td>
<td>440±75</td>
<td>405±65</td>
<td>375±40</td>
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<tr>
<td>LV MAPD</td>
<td>380±60</td>
<td>440±60*</td>
<td>410±50</td>
<td>350±60**</td>
</tr>
<tr>
<td>RV MAPD</td>
<td>320±45</td>
<td>350±55</td>
<td>330±60</td>
<td>310±40</td>
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<tr>
<td>ΔMAPD</td>
<td>60±30</td>
<td>90±15*</td>
<td>80±15</td>
<td>40±25**</td>
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</table>

*a All values in ms. * P<0.01 SCD vs. non-SCD; ** P<0.05 SCD and TdP responders vs. non-responders.

3.2. TdP responder versus non-responder group

Twenty four dogs met the inclusion criteria of which 15 received almokalant and nine ibutilide. Half of them (n=6 ibutilide, n=6 almokalant) responded with TdP to the drug challenge (i.e. TdP responders) while the other half did not (non-responders).

As previously described [8,9] and visualized in Fig. 3, class III drugs increased significantly (1) CL-IVR, (2) QT-time, and (3) all MAP-derived durations, including ΔMAPD (data not shown).

3.3. Arrhythmogenic and electrophysiological parameters of the subgroups at baseline: SCD, TdP responders and non-responders

In Table 1 (right part), the electrophysiological parameters of the SCD group, TdP responders and non-responders at baseline are compared. No significant differences existed between the three subgroups in CL-IVR, QT-time and RV MAPD. LV MAPD and ΔMAPD were however significantly different between the SCD and TdP responders versus non-responders. Although LV MAPD and ΔMAPD were both significantly increased in the SCD group compared to the non-SCD group, the ΔMAPD between the SCD and TdP responders was not significantly different from the ΔMAPD between the SCD and non-SCD group. This suggests that the arrhythmogenic substrate in the SCD group is more pronounced than in the non-SCD group.

Fig. 2. Representative example of torsade de pointes arrhythmia at baseline conditions. Lead II of the surface ECG and the left (LV)- and right (RV) ventricular monophasic action potential (MAP) were recorded simultaneously at a paper speed of 10 mm/s. Under baseline conditions the values of LV MAPD (520 ms) and ΔMAPD (LV minus RV MAPD=75 ms) were already pronounced. One spontaneous ectopic beat (asterisk) was sufficient to trigger a torsade de pointes arrhythmia which in this case terminated spontaneously.
ΔMAPD appeared somewhat larger in the SCD compared to the TdP responder group, these differences did not reach significance. Fig. 4 shows the individual data points of the ΔMAPD in the three groups, which revealed clearly the distinction between the SCD and TdP responder groups on the one hand versus the non-responder group on the other. Thus, in fact we can distinguish two groups: arrhythmogenic and non-arrhythmogenic, on the basis of their LV MAPD and ΔMAPD during baseline. In Table 2, the different specificity and sensitivity values for ΔMAPD cut-off points of 40, 65, and 90 ms can be seen in relation to the occurrence of ventricular arrhythmias.

4. Discussion

This study demonstrates that in the dog with CAVB, SCD can most probably be attributed to (polymorphic) ventricular tachycardias. The ability to induce TdP at baseline and the measure of LV MAPD and ΔMAPD indicate susceptibility to SCD.

4.1. Telemetry device

The observation period started following the electro-physiological study, which was performed after at least 4 weeks of CAVB. From this time on, we assume that the (electrical) remodeling processes are completed and stable in time [11,12].

To record the mode of death, we developed a telemetry system which provides a two-lead ECG recording for 24 h a day for a maximum of 2 months in a dog which can move freely in his cage. The first analysis of these telemetry recordings in the two dogs dying suddenly, revealed in both cases that the arrhythmia was preceded by an acceleration in idioventricular rhythm which was accompanied by ventricular ectopic activity (Fig. 1). The latter pattern shows similarities with the initiation sequence of drug-induced TdP (Fig. 3) in which EADs trigger ectopic beats, setting the stage for a TdP arrhythmia. The observed acceleration in rate and the fact that the two witnessed deaths occurred when the dogs were excited suggest an adrenergic contribution to the initiation of the arrhythmia.

4.2. Predictive parameters of SCD

In our retrospective study we looked at 78 CAVB dogs, including eight SCD dogs. The group of 24 dogs which
Interestingly the SCD group and the TdP responder group show many similarities. The ΔMAPD at baseline of these two groups was significantly different from the non-responder group (Table 1 and Fig. 4). A ΔMAPD of ≥65 ms had a sensitivity of 85% and a specificity of 92% for the occurrence of ventricular arrhythmias (Table 2). Besides ΔMAPD, the only other electrophysiological parameter which showed a significant difference was LV MAPD. This suggests that the length of the LV MAPD plays an important role, either in creating dispersion between the ventricles (ΔMAPD) or in generating early afterdepolarizations triggering arrhythmias [16,17]. It was surprising to find that QT-time did not discriminate sufficiently to become predictive. Also CL-IVR was similar in the different group comparisons excluding bradycardia as an arrhythmogenic factor.

4.3. Basis of the enhanced sensitivity to SCD in the CAVB dog

QT prolongation or repolarization lability are regarded as risk factors for ventricular arrhythmias and SCD in patients with cardiac hypertrophy or failure [18]. Recently the concept of a decreased repolarization reserve was introduced [19,20]. Arrhythmias would then occur when the reduced repolarization is challenged, e.g. by drugs or adrenergic stimulation [19–21].

We have described that the prolonged repolarization in SCD and the TdP responder groups.

Fig. 4. Individual ΔMAPD (y-axis) data of the three subgroups: sudden cardiac death (SCD), TdP responder and non-responder groups. A clear distinction in ΔMAPD can be seen between the SCD and the TdP responder groups on the one hand versus the non-responder group on the other. This is indicated by the term arrhythmogenic which combines the SCD and the TdP responder groups.

received almokalant or ibutilide, showed a TdP responders versus non-responders ratio comparable to other anti-arrhythmic drugs used in the model [10].

An arrhythmogenic parameter indicative of SCD was the ability to evoke TdP already under baseline circumstances. In some anesthetized dogs TdP arose spontaneously (Fig. 2), while in others our short-long-short mimicking pacing protocols were able to initiate TdP.

One of the other electrophysiological parameters we focused on was ΔMAPD, as we recently demonstrated that the amount of ΔMAPD is strongly associated with drug induced TdP [1,8–10]. Also in other models of hypertrophy and heart failure, inter- and intraventricular inhomogeneity in action potential duration has been described [13,14], while Antzelevitch et al. [15] described the concept of transmural dispersion of repolarization. In Table 1 it can be seen that the ΔMAPD of the SCD group is significantly larger compared to the non-SCD group.

Table 2

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4.4. Relevance of the model

Only few studies have been able to demonstrate arrhythmogenic consequences of the mentioned repolarization abnormalities in hypertrophy and heart failure [13,14,22–26]. The presumed adrenergically induced TdP in the conscious CAVB dog in which the I\(_K\) current is decreased shows similarities with some forms of the congenital long QT syndrome (LQT1 and LQT2) in which SCD is related to I\(_{Kr}\) or I\(_{Ks}\), downregulation and adrenergic stimulation [27]. Also patients with 'forme fruste' congenital LQT syndrome show an increased TdP susceptibility to class III drugs [28].

5. Limitations

SCD is a complex phenomenon whose appearance is unpredictable. In this respect our follow-up period of ≥4 weeks could have been too short. The scope of the study prevents us from drawing conclusions about the cause of the increased susceptibility to SCD in a subgroup of CAVB dogs. Cellular electrophysiological studies on sudden death could not be performed because cells can only be obtained from freshly arrested hearts. Placement of MAPs at only two sites (LV and RV) ignores possible transmural and intraventricular differences. However, we have shown with multisite transmural needle electrodes that ΔAPD is present within the CAVB dog heart [29].

6. Conclusion

In the CAVB dog model, SCD is (1) most probably related to TdP while (2) inducible TdP and the measure of LV MAPD and ΔMAPD at baseline indicate susceptibility to SCD.

Acknowledgements

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