THE RELATIONSHIP BETWEEN EARLY AFTERDEPOLARIZATION AND THE OCCURRENCE OF TORSADES DE POINTES
— An In Vivo Canine Model Study —

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The relationship between early afterdepolarization (EAD) and the occurrence of torsades de pointes (TdP) was studied in a canine model. Twelve dogs of both sexes, weighing 9.9–16 Kg, were studied. After reducing the concentration of serum potassium to 3.0–4.0 mEq/l, by administration of calcium polystyrene sulfonate at 15–20 g/day for 1 or 2 weeks, a 6F electrode catheter was introduced via the femoral vein and positioned at the atrioventricular (AV) junction. Complete AV block was produced by catheter ablation using a high frequency current. A Franz 6F catheter was introduced into the right ventricle to record monophasic action potentials (MAPs) using the contact electrode technique. After a stable recording of the MAPs was achieved, cesium chloride (CsCl; 1 mM/Kg) was administered as an intravenous bolus over 15 sec. The MAPs and electrocardiogram (ECG) changes were simultaneously recorded for 30 min after the administration of CsCl. The administration was repeated several times at intervals 30 min. Sustained or non-sustained ventricular tachycardia was produced in all dogs. EAD appeared in 8 of 12 dogs. When EAD developed sufficiently high amplitude, ventricular premature beats occurred near the peak of EAD and TdP was induced in 3 of 8 EAD-positive dogs. TdP was not induced in EAD-negative dogs. Although TdP was comparatively difficult to induce, EAD-triggered activity was suggested to be one of the necessary conditions for TdP, because TdP occurred only when EAD reached a sufficiently high amplitude to produce ventricular premature beats.

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AFTERDEPOLARIZATIONS have recently been suggested as a possible cause of cardiac arrhythmias that cannot be explained by reentry or abnormal automaticity under various conditions. The response of arrhythmia to pacing has been used to differentiate reentrant rhythms from non-reen-

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EADs have been defined by Cranefield\textsuperscript{14} as a depolarizing afterpotential that interrupts or delays normal repolarization of phase 3 of the cardiac action potential. EADs have been induced in isolated cardiac tissue under a variety of conditions that increase inward current or reduce repolarizing current. These conditions include exposure to catecholamines, hypokalemia\textsuperscript{6} acidosis\textsuperscript{15} hypoxia\textsuperscript{16} and exposure to many drugs such as aconitine\textsuperscript{17} quinidine\textsuperscript{8} disopyramide\textsuperscript{9} sotalol\textsuperscript{10} and cesium chloride\textsuperscript{2,13,18} The purpose of this study was to examine whether TdP could be induced from EADs in an in vivo canine model using cesium chloride with simultaneous recording of monophasic action potentials (MAPs) and surface electrocardiograms (ECGs).

\textbf{MATERIALS AND METHODS}

Twelve adult mongrel dogs of both sexes weighing 9.9—16 kg were anesthetized with sodium pentobarbital (30 mg/kg) and ventilated with room air using a constant-volume ventilator. A 6F electrode catheter (HAT 260) was introduced to the atroventricular (AV) junction via the femoral vein and radio-frequency energy was delivered from the tip of the catheter to produce complete AV block using a radio-frequency generator (HAT 200, 520 KHz, Opyska). After complete AV block was produced, calcium polystyrene sulfonate was given at 15—20 g/day for 1 or 2 weeks to reduce the potassium concentration to a range of 3.0—4.0 mEq/l.

MAPs were recorded using Franz’s\textsuperscript{19} electrode catheter, which was introduced via the femoral vein and positioned on the right ventricular endocardium by the contact electrode technique. This catheter was able to pace the right ventricle while simultaneously recording MAPs. Right ventricular (RV) pacing was performed at a twofold diastolic threshold with a square wave pulse. After a stable recording of MAPs was obtained, cesium chloride (CsCl; 1 mM/kg) was administered as an intravenous bolus over 15 seconds via a central venous catheter positioned in the femoral vein. MAPs and the activities from surface ECG leads I,II,III and V\textsubscript{1} were recorded simultaneously for 30 min. In the case of cardiac arrest, constant pacing of right ventricle at a pacing cycle length of 2,000 msec was continued until a spontaneous ventricular rhythm reappeared. This procedure was repeated every 30 min as long as a stable recording of MAPs could be obtained.

According to Brachmann et al\textsuperscript{2} the effect of cesium lasts for approximately 20—30 min. Therefore, the cesium chloride was administered every 30 min. When EADs of the type defined by Cranefield\textsuperscript{14} appeared,
the responses of the EADs to pacing were evaluated. This pacing consisted of premature stimuli and constant stimuli in order to differentiate the EADs from artifacts. After every five drive stimulus at the basic cycle length ($S_1S_1 = 1500$ ms), single premature stimuli ($S_2$) were introduced with incremental coupling intervals of 800, 700, 600, 500, and 400 ms. Conversely, overdrive pacing was performed incrementally at cycle lengths of 800, 700, 600, 500, and 400 ms. The MAPs and surface ECGs were simultaneously recorded on a thermal recorder at a paper speed of 50 mm/sec. The MAP signals were amplified at a frequency of 0.1–10 kHz. The baseline of the MAPs appeared to be relatively stable, although atrial potentials and artifacts caused by respiratory movements were observed during marked bradycardia after the CsCl administration. These artifacts, however, were considered negligible, because the EADs could be differentiated from them by the ventricular pacing method and the artifacts were thought to be too small to influence the RV MAPs. The QT intervals were not measured in this study.

**RESULTS**

*Response of EADs to pacing*

Fig. 1 shows complete AV block at a ventricular rate of 54 beats/min induced by radio-frequency catheter ablation at the AV junction. MAPs were recorded simulta-
### TABLE I

<table>
<thead>
<tr>
<th>No</th>
<th>EAD</th>
<th>VT</th>
<th>K (mEq/l)</th>
<th>CsCl (times)</th>
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<td></td>
<td></td>
<td>MTV</td>
<td>PVT</td>
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</tr>
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<td>12</td>
<td>+</td>
<td>+</td>
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</tr>
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</table>

*Early afterdepolarization (EAD), ventricular tachycardia (VT) are indicated as positive (+) when present. Monomorphic ventricular tachycardia and polymorphic ventricular tachycardia are designated by MVT and PVT, respectively. Serum potassium concentration is designated as K. The number of cesium chloride (CsCl) injection is expressed as "(times)"."

by S2 was progressively attenuated. When the S1S2 interval was shortened to 500 msec, the amplitude of the EAD decreased markedly (Fig. 2B). The response of EADs to constant pacing was similar to that of the extrastimulus testing, i.e., pacing at a short cycle length led to EAD amplitude attenuation. Fig. 3 shows the recordings of two pacing cycle lengths (PCL). EADs were clearly observed on MAPs at a PCL of 900 msec (Fig. 3A). As the PCL was shortened, the amplitude of the EADs was progressively attenuated and eventually could not be recognized, as shown in Fig. 3B (PCL=500 msec).

**EAD-induced triggered activity**

Table I summarizes the data for the 12 experiments. Ventricular tachycardia (VT) was induced in all 12 dogs. The polymorphic ventricular tachycardias (PVTs) are defined below for ease of discussion. When more than two morphologies of the QRS complex are recognized during VTs without changing the QRS axis, they are defined as PVTs. If the twisting of the QRS complex was observed during PVTs, they were defined as Tdp. Sustained monomorphic ventricular tachycardia (MVT) alone was induced in 6 dogs. Both monomorphic and polymorphic VT were induced in 5 dogs. Polymorphic ventricular tachycardia (PVT) alone was induced in 1 dog. PVTs therefore appeared in 6 dogs, and Tdp was induced in 3 of these 6 dogs. Ventricular fibrillation (Vf) requiring cardioversion was induced in 7 dogs. Analysis of the MAPs revealed that EADs appeared in 8 of 12 dogs after the administration of CsCl. EADs were not induced in the remaining 4 dogs despite repeated injection of CsCl. In the EAD-induced group, MVT was induced in 5 dogs, but Tdp was not induced in these dogs. Both MVT and PVT were induced in 2 dogs, with Tdp also present in these dogs. Both PVT and Tdp were induced in the remaining dog. Thus, Tdp was induced in 3 of 8 EAD-induced dogs. On the other hand, in the group without induced EAD, MVT was induced in one dog and both MVT and PVT were induced in 3 dogs. Tdp however, was never induced in this group. Tdp was induced only in EAD-positive dogs. Vf was induced in 5 of 8 EAD-induced dogs, and in 2 of 4 dogs with-
out induced EAD. No difference between the two groups was observed in the incidence of Vf. Serum potassium concentration ranged from 3.1 to 3.9 mEq/l. The incidence of PVT was not related to the serum potassium concentration within this range.
Fig. 6. Torsades de Pointes induced by cesium chloride
Polymorphic ventricular tachycardia with the QRS complex twisting around
the baseline was induced after the administration of cesium chloride. A ventricular
ectopic beat occurred near the EAD peak and the following EADs repeatedly
produced ventricular ectopic beats. This suggests that triggered activity may be
associated with the genesis of torsades de pointes.

Fig. 7. Monomorphic ventricular tachycardia induced by cesium chloride
EADs were recognized on the MAPs, but were not related to the genesis of
monomorphic ventricular tachycardia. Monomorphic ventricular tachycardia
occurred from phase 4 of the MAP.

Approximately 30 min were needed for spontaneous recovery of the ventricular
rhythm in this bradycardia model, and it is believed that the effect of CsCl lasts
for 20–30 min.12 Although the amplitude of the MAPs diminished as the dose of
CsCl increased, each dog received 2–4 injec-
tions.

EADs induced by the administration of cesium ceased within 15 min in almost
all cases. However, the amplitude of the
EADs that developed was progressively
augmented for several minutes after injec-
tion. Ventricular ectopy appeared when
the amplitude of the EADs appeared to
reach a threshold potential. Fig. 4 shows a
typical example in which triggered action
potentials were induced in bigeminy when
the amplitude appeared to reach a threshold
potential. A ventricular ectopy disap-
peared in the sixth beat although the am-
litude of the unfired EAD on the MAP was
similar to that of the fired EADs. This
EAD, which appeared to reach the threshold
potential, may not have fired because the
focus of triggered activity may have been
slightly distant from the MAP recording
site. The EADs that reached the threshold
potential induced two, rather than just one,
triggered action potential, which corres-

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responded to ventricular ectopy on surface ECGs. By contrast, when subthreshold EADs induced by CsCl were not able to produce triggered action potentials, no ventricular ectopy appeared on surface ECGs (Fig. 5).

TdP occurred only when EADs appeared and repeatedly reached the threshold potential to induce a triggered action potential. Fig. 6 presents one example of TdP induced by cesium administration. In this example, the first ectopic ventricular firing was induced by EADs that reached the threshold potential, while subsequent ventricular firings were observed where the morphology of the QRS complex twisted around the axis on surface ECGs.

Ventricular tachycardia not related to EADs

MVTs were induced by cesium injection in 11 of 12 dogs. In all cases, these MVTs seemed to have no relation to EADs. Fig. 7 presents one example of MVT which occurred after an action potential had returned to the resting potential (phase 4) despite the appearance of EADs on the MAPs. Fig. 8 shows another example of MVT. In this case, MVT occurred when an EAD did not appear on the MAPs, and began from phase 4 of a MAP. These two examples suggest that MVTs can be induced whether or not EADs are present.

**DISCUSSION**

The present study was designed to test the hypothesis that cesium-induced multiform ventricular tachycardia, (TdP) is caused by bradycardia-dependent EADs and triggered activity.

**Induction of EADs in an in vivo animal model**

Various methods have been used to induce bradycardia, including injection of formaldehyde into the AV junction and ligation of the right coronary artery. However, these conventional methods are both laborious and time-consuming. The present study used radio-frequency catheter ablation to interrupt AV conduction, which allowed relatively easy and rapid interruption of the AV junction.

Earlier studies reported that pacing at a short cycle length led to an attenuation of EADs. Accordingly, the response to pacing was thought to be useful to differentiate EADs from artifact. In our experiments, the characteristics of cesium-induced EADs were similar to those observed in earlier studies.

In vivo experiments, Damiano and Rosen showed that CsCl produced EADs at both “low” and “high” membrane potentials, but triggered activity was induced only at “high” membrane potentials. They dem-
onstrated that a “high” membrane potential EAD interrupting phase 3 occurred with hypokalemia, whereas a “low” membrane potential EAD interrupting phase 2 occurred with normokalemia. We decided to inject CsCl, since it was difficult to induce EADs and triggered activity with only bradycardia and hypokalemia. Since the serum half-life of CsCl was reported to be approximately 5 min! it was assumed that most of the injected CsCl would be cleared from the blood within 20 min. However, intracellular levels remain at a steady state for 30 min after injection and intracellular accumulation may occur with subsequent injection. For this reason, CsCl was injected every 30 min as long as a response to the injection was observed.

The role of CsCl-induced EADs in the genesis of ventricular ectopic activity

The ventricular premature beats did not occur until the amplitude of the induced EADs increased sufficiently, suggesting that the premature beat might result from a threshold response. According to the definition of EADs developed by Damiano and Rosen, this type of EAD was thought to be a “high” membrane potential EAD, since they occurred from phase 3 on the MAP, although the potential was not measured. It was therefore supposed that “high” membrane potential EADs produced by CsCl could induce triggered activity. The ventricular ectopy could not be observed as the amplitude of the EADs decreased over time. This fact strongly suggested that the occurrence of ventricular ectopy was due to the EADs. EADs are known to develop in vitro in ventricular muscle or Purkinje fibers exposed to drugs or other conditions that cause prolongation of the repolarization phase. It is thought that the genesis of EADs is related to the depression of potassium currents. However, definite evidence for the ionic current alteration in the production of EADs was not found.

On the other hand, Brugada and Wellens suggested that when EADs at “low” membrane potentials developed in one area, they resulted in prolonged repolarization and differences in the potentials of adjacent areas. This voltage gradient could create a “boundary” current that could electrotonically depolarize another area. Brugada and Wellens called this mechanism “prolonged repolarization-dependent reexcitation”. However, none of the findings in the present study support this hypothesis.

EADs were induced in 8 of 12 dogs in the present study. In those cases in which EADs could not be induced the catheter in the right ventricle was most likely not in the area where EADs could be detected, since previous studies have reported that the amplitude of EADs differed according to the ventricular sites.

CsCl-induced TdP and the relationship between TdP and EADs

The present study has demonstrated that TdP, i.e., polymorphic ventricular tachycardias with twisting of the axis of the QRS complex continuously on surface ECGs, developed from either the EAD peak or from its vicinity, and further, that it corresponded to ventricular premature beats with a shorter coupling time on surface ECGs. This fact suggests that the first ectopic beat is triggered by an EAD. However, the mechanism of subsequent beats of ventricular tachyarrhythmias is not clear. There was some evidence in vitro that the second and subsequent ventricular beats were also triggered by EADs, which was not clearly evident in vivo. The phenomenon that TdP initiated from the EAD peak or its vicinity reaching the threshold potential, and the fact that it was terminated when the amplitude of the EAD decreased below the threshold potential, strongly supports the hypothesis that the TdP was due to triggered activity by EADs. However, we could not exclude the possibility that subsequent ectopic beats during TdP were due to reentry caused by inhomogeneity of refractoriness. Although the initiating mechanism of ventricular tachycardia is considered to be EADs, different factors, such as variations in autonomic tone, may be required to sustain the arrhythmia. Hanich et al reported that ventricular tachycardias, which could not be induced after the first injection of CsCl, could be induced again after stellate stimulation and before the next injection of CsCl. They demonstrated that the autonomic nervous system modulated ventricular tachycardias, while only slightly affecting the amplitude of
EADs.

It has been difficult to understand the mechanism of the twisting of the QRS complex characteristic of TdPs. In this experiment, MAPs were recorded at one site although this phenomenon could not be analyzed without more than three MAPs recording sites. When EADs appeared at many sites in various degrees, the electrical gradient was though to occur between any two sites. If the repolarization phase was prolonged by the occurrence of EAD at one site, and it was not prolonged at any other sites because of little or no EAD, the electrical gradient might be produced among them and might depolarize other sites which recovered excitability in an irregular manner. If more than two sites were able to be activated irregularly by this electrical gradient mechanism, polymorphic tachycardia with continuous changes in the QRS complex might occur. While this mechanism was reported to be one reason that the QRS complex twists around the axis in TdPs, it could not be proven in the present study. The TdPs induced in the present experimental model were similar to those induced in other models\textsuperscript{12,13,22} and clinical cases since their occurrence was dependent on bradycardia and since they had the morphology of the QRS complex twisting around the baseline on surface ECGs. However, other in vivo experiments and clinical cases have reported that TdPs were not induced from bradycardia-dependent EADs. We were able to demonstrate not only that premature ventricular beats were correlated with EADs, but also that PVTs with the QRT complex twisting around the baseline, were induced from EADs in an in vivo experimental model.

Although TdP was not easily induced in this experiment, TdP was induced only when EADs were recognized and their amplitude reached the threshold potential. On the other hand, MVTs were easily induced independent of EADs. In summarized data, MVTs were thought to be induced when EADs occurred, but these EADs were induced by repeated injection of CsCl. When MVTs were induced, they appeared from phase 4 of the MAPs on which EADs were not recognized or for which the amplitude was too small, had they been recognized.

Therefore, we concluded that MVTs were induced regardless of the occurrence of EADs. PVTs were also thought to occur regardless of EADs, since PVTs were induced from phase 4 of the MAPs in 3 of the dogs in which EAD was not induced.

These facts strongly suggest that the mechanism of TdP is different from that of MVTs and PVTs. The relationship between a serum potassium concentration of 3.0–4.0 mEq/l and the occurrence of TdP was not clear from the present study.

CONCLUSION

Torsades de pointes was induced near the peak of EADs in an in vivo AV block dog model after the administration of cesium chloride.

Monomorphic ventricular tachycardias were induced independent of EADs. These findings strongly suggest that the mechanisms of these two ventricular tachycardias are different and that the genesis of torsades de pointes might be bradycardia-dependent EAD.

REFERENCE

2. ROSEN MR, REDER RF: Does triggered activity have a role in the genesis of cardiac arrhythmias? Ann Intern Med 1981; 94: 794–801
9. SASYNLUK BJ, VALOIS M, TOY W: Recent advances in understanding the mechanism of drug-induced torsades do Pointes arrhythmias. Am J Cardiol 1989; 64: 293—323


17. SCHMIDT RF: Versuche mit Aconitin zum Problem der spontanen Erregungsbildung im Herzen. Pflugers Arch 1960; 271: 528—506

18. ISENBERG G: Cardiac Purkinje fibers: Cesium as a tool to block inward rectifying potassium currents. Pflugers Arch 1976; 365: 98—106


