Bradycardia-dependent triggered activity: relevance to drug-induced multiform ventricular tachycardia

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ABSTRACT We used cesium chloride (CsCl) for electrophysiologic studies in canine hearts in vivo and in vitro to examine the mechanisms underlying ventricular arrhythmias that are related to prolonged repolarization. Cesium is known to depress normal ventricular automaticity and some experimental arrhythmias by blocking delayed outward currents and prolonging action potential duration. In 10 dogs in normal sinus rhythm, 1 to 1.5 mM/kg iv CsCl prolonged the QT (QU) interval and induced ventricular ectopy in all, including multiform ventricular tachycardia. In 12 dogs with atroventricular block, 1 to 1.5 mM/kg iv CsCl produced marked suppression of idioventricular rates (from 45 ± 6 to 8 ± 4 beats/min). These low rates were then associated with bigeminy or bursts of multiform ventricular arrhythmia. Pacing at rates of 60 beats/min or more suppressed these arrhythmias. Low doses of tetrodotoxin (1 μg/kg) also abolished these bradycardia-dependent arrhythmias without affecting the amplitude of ventricular electrograms. Tissue concentrations of cesium were determined by anatomic absorption spectroscopy in five dogs after injection of 1 mM/kg CsCl. Thirty minutes after the injection, cesium levels in Purkinje fibers were 5.3 ± 1.0 mM/kg, levels in ventricular muscle were 4.6 ± 0.9 mM/kg, and levels in atrial muscle were 4.1 ± 0.8 mM/kg. In eight isolated endocardial preparations from canine ventricles, standard microelectrode techniques were used to study the effects of superfusion with 5 mM cesium. After 30 min, we observed early afterdepolarizations interrupting phase 3 of Purkinje fiber action potentials that already showed prolonged repolarization. Slowing the rate generated single or multiple action potentials arising from partially repolarized levels of membrane potentials (−80 to −65 mV). Pacing rates of 30 to 60 beats/min diminished the afterdepolarizations and suppressed the spontaneous beats. Tetrodotoxin at a concentration of 10−8 g/ml, which did not affect upstroke velocity, abolished the afterpotentials. We conclude that cesium induced bradycardia-dependent ventricular arrhythmias caused by early afterdepolarizations. These data suggest that an inward current, probably carried by sodium ions, appears to be essential for the occurrence of this phenomenon. The association of delayed repolarization, afterdepolarizations, and triggered activity has similarities to the phenomenon of drug-induced prolongation of the QTU interval associated with multiform ventricular tachycardia in humans, i.e. "torsades de pointes."

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IN THE PAST DECADE, information has been accumulating on the occurrence of afterdepolarizations and triggered activity in cardiac tissue and their possible role in the generation of cardiac arrhythmias under various experimental conditions. A substantial amount of data concerning delayed afterdepolarizations has been acquired from experiments with preparations in vitro that were exposed to cardiac glycosides or catecholamines.1–9 Also, triggered activity due to delayed afterdepolarizations has been observed in recordings from the canine coronary sinus10 as well as in the canine, simian, and human mitral valve muscle.11–13 A common denominator for these triggered arrhythmias due to delayed afterdepolarizations has been their tachycardia-dependent mode of induction. This electrophysiologic behavior has been used to establish rules by which arrhythmias due to delayed afterdepolarizations in patients could be detected.14 Observations on delayed afterdepolarizations induced by cardiac glycosides in voltage-clamp experiments provided evidence for a transient mixed inward current due to an increase in membrane permeability mediated by oscil-
lation in cytosolic calcium. This hypothesis was substantiated by the finding that triggered activity was suppressed by calcium-blocking drugs (e.g., verapamil) and by high concentrations of the fast channel-blocker tetrodotoxin (TTX).

Because delayed afterdepolarizations generally have shown a tachycardia dependence, they are not a likely mechanism for bradycardia-dependent arrhythmias. The mechanisms for bradycardia-dependent arrhythmias have attracted relatively little attention. The observation that bradycardia leads to a lengthening and a greater variation of the relative refractory periods throughout the heart has focused emphasis on reentrant mechanisms in the genesis of tachyarrhythmias that are bradycardia-dependent. Bradycardia-dependent ventricular ectopy has been observed for many years in association with complete heart block in humans and in other settings. Also, in recent years considerable attention has been directed to the intriguing association of prolonged QT intervals and multi-arrhythmias, called torsades de pointes, induced by certain antiarrhythmic drugs as well as by other factors. It has been observed that in these circumstances the ventricular ectopy appears to be exacerbated by long RR intervals, i.e., bradycardia dependence. To clarify the cellular electrophysiologic mechanisms underlying the association between delayed repolarization (prolonged QT interval), ventricular ectopy, and bradycardia dependence, we observed the effects of cesium under conditions of varying heart rates. Cesium is known to delay repolarization by blocking potassium currents. Our observations of the arrhythmogenic properties of cesium in the experimental setting support a concept of bradycardia-dependent triggered activity caused by early afterdepolarizations that are accompanied by a marked prolongation of repolarization. We hypothesize that a similar mechanism may operate in patients with drug-induced long QT intervals and associated ventricular tachyarrhythmias.

**Methods**

**In vivo experiments.** Adult mongrel dogs weighing 10 to 20 kg were anesthetized with sodium pentobarbital (30 mg/kg, iv) and were artificially resired with room air. A jugular vein was cannulated for intravenous administration of drugs, and left ventricular pressure was monitored through a polyethylene catheter advanced into the left ventricle via the left common carotid artery. An electrode catheter with ring electrodes 10 mm apart was inserted into the right common carotid artery and advanced into the noncoronary cusp of the aortic valve to record His bundle activity. Vagal-induced slowing of the heart rate was used to determine underlying idioventricular automaticity before complete heart block was induced. Vagal-mediated slowing was accomplished by insertion of silver wires into the cervical vagosympathetic trunk. Square wave pulses of 0.05 msec were delivered at 1 to 20 V and at a frequency of 20 Hz. A thoracotomy was performed in the right fourth intercostal space, and the lateral surface of the right atrium and basal portions of the right ventricle were exposed. Bipolar electrodes consisting of pairs of stainless steel wires (0.005 inches in diameter) were inserted into the right atrial appendage and into the right ventricular outflow tract to provide atrial and ventricular stimulation, respectively, and to record electrograms. Pacing was achieved by delivery of electrical pulses of 2 to 10 V of 2 msec duration with an S-88 Grass stimulator and a SIU-5 isolation unit. Complete heart block was achieved by injection of 0.3 to 0.5 ml of 37% formaldehyde into the AV node. Regular idioventricular rhythms obtained by vagal stimulation or complete atrioventricular (AV) block showed no significant difference, except for transient ventricular ectopy associated with local damage to the ventricle on occasion. Within 2 to 5 min this intermittent activity disappeared.

Electrocardiographic lead II, His bundle electrogram, and left ventricular pressure were continuously monitored. However, the latter was displayed intermittently on the actual recordings. All records were obtained on a multichannel oscilloscopic photographic recorder (Electronics for Medicine, VR-12) at paper speeds of 10 to 100 mm/sec. In addition, continuous recordings were made in each experiment on a multichannel magnetic tape recorder (Hewlett-Packard eight-channel) so that sections could be replayed for analysis and for photography.

In dogs with heart block, ventricular pacing was achieved and the responses to single and repetitive stimulation at rates from 10 to 240 beats/min were determined. When no spontaneous ventricular rhythm was present for periods longer than 20 sec, basic pacing at 20 beats/min was introduced. Cesium chloride (CsCl) (0.25 to 1.0 mM/kg) was administered intravenously in one or two doses. At a total dose of 1 to 2 mM/kg, ventricular bigeminy or multiple ventricular ectopic beats were observed.

The response to the pacing protocol was again determined. Thereafter, TTX was given as a 1 μg/g bolus injection and the stimulation procedure was repeated.

Tissue and plasma levels of cesium were determined in five animals by atomic absorption spectroscopy. Control samples were obtained from the blood and from the right atrial appendage to allow for repetitive measurements of tissue levels without serious impairment of cardiac function. Each incision was closed by silk ligature, and the tissue sample was resected from an intact area of the appendage to prevent impairment of its blood supply. Sampling was repeated at various times 1 to 30 min after intravenous administration of 1 mM/kg CsCl. Subsequently, the heart was removed and additional samples were excised from free-running Purkinje strands and left ventricular myocardium; the samples were blotted before being weighed.

We diluted 10 ml of plasma with 4.0 ml of deionized water and vortexed it for 10 sec before analysis. Small quantities of tissue (approximately 50 mg) were accurately weighed and 3.0 ml of deionized water was added. This material was homogenized for 75 to 90 sec, then centrifuged at 2000 g for 30 min. The supernatant was analyzed with a Varian 1200 Atomic Absorption Spectrophotometer equipped with a cesium hollow lamp. Cesium levels were determined at a wavelength of 852.1 nm with a spectral bandwidth of 2.0 nm. A standard curve was established with calibrated standards ranging from 1 to 25 μg/ml. The samples were analyzed, and results were obtained from the generated standard curve. The concentrations of cesium present were expressed as mM/l in the plasma and mM/kg in the tissue.

**In vitro experiments.** Preparations were isolated from eight mongrel dogs. After anesthesia with sodium pentobarbital (30 mg/kg, iv), a thoracotomy was performed and the hearts were...
rapidly removed and dissected at room temperature in a physiologic solution of the following composition (mM): Na⁺ 151.0, K⁺ 4.0, Ca²⁺+ 1.35, Mg²⁺+ 0.5, Cl⁻ 131.0, HCO₃⁻ 24.0, H₂PO₄⁻ 1.8, and dextrose 5.5. The solution was equilibrated with a gas mixture of 95% O₂-5% CO₂. Preparations containing Purkinje and myocardial cells, usually including a free-running strand, were dissected from the left ventricular endocardium. The preparation was placed into a wax-based tissue bath and superfused with a physiologic solution at 35° to 37°C. We added CsCl in a range of concentrations from 0.25 to 20 mM, but the observations in this report generally were made with a concentration of 5 mM, which most readily resulted in the generation of afterdepolarizations and triggered activity. The tissues were stimulated through bipolar electrodes placed on Purkinje fiber strands. Stimuli were rectangular pulses of 2 msec duration and variable frequency and amplitude, delivered from pulse generators triggered by ramp generators through a stimulus isolation unit (Tektronix series 2600). Pacing protocols were similar to those in vivo and included rates from 30 to 240 beats/min. We used standard techniques to record intracellular and extracellular potentials. Intracellular potentials were recorded through glass capillary microelectrodes with a tip resistance of 10 to 30 megohms and filled with 3M potassium chloride. The first stage amplifier had high-input impedance (10¹⁴ ohms), negative capacitance feedback, and a gain of 10.

Extracellular potentials were recorded with bipolar electrodes of fine (diameter 0.003 inches) Teflon-coated stainless steel wires bared at the tips. The wires were led into differential amplifiers with a gain of 200. The preamplified signals were led into an oscilloscope with eight input channels and a dual time base (Tektronix series 5100). The upstrokes of action potentials were differentiated with a resistance-capacitance circuit or operational amplifier that was linear up to 1000 V/sec. Conduction times were measured as the intervals between activation of two close bipolar electrodes placed along a direction perpendicular to the wavefront of excitation. The duration of action potentials was measured to 100% repolarization. Often intracellular recordings were made from two cells widely separated in the preparation (1 to 3 cm apart) to determine whether the changes observed were widely distributed throughout the preparation.

**Statistical analysis.** Comparisons among different drugs were performed by means of a 2-way analysis of variance. The significance level for the probability (p) was set at .05. All values were expressed as means ± SD.

**Results**

In vivo experiments. Our preliminary reports have indicated that CsCl in doses of 0.05 to 0.25 mM/kg iv strongly suppresses ventricular automaticity in canine hearts in situ (figure 1). Figure 1, A, shows a regular idioventricular rhythm at a rate of 42 beats/min after introduction of complete AV nodal block. Within 2 min after CsCl, marked slowing of the spontaneous firing in the ventricles occurred. The effect is shown in figure 1, B, by cessation of activity after the fourth beat. After another minute, a slow escape rhythm at a rate of 6 beats/min resumed.

At higher concentrations of CsCl, we invariably observed the occurrence of ventricular arrhythmias. In animals in normal sinus rhythm, the ventricular tachyarrhythmias occurred within 30 sec of the rapid intravenous administration of 1 to 1.5 mM/kg CsCl and lasted for several minutes. Tachyarrhythmias were observed in 10 animals in sinus rhythm, varying from bigeminal premature ventricular contractions to runs of multiform ventricular tachycardia, sometimes leading to ventricular fibrillation, which usually occurred at doses of 1.5 mM/kg or more. A representative example is shown in figure 2. Note the sinusoidal pattern of changing QRS and T axes resembling the clinical arrhythmia, torsades de pointes. A slowing of the sinus rate preceded the onset of ventricular ectopy. Since the

**FIGURE 1.** Effect of CsCl on normal ventricular automaticity in the intact heart after complete AV nodal block. A, Regular but dissociated atrial and ventricular electrograms recorded by an electrode catheter at the AV junction (HBE) and electrocardiographic lead II (L2). The respective rates are 150 and 45 beats/min. B, After administration of 0.25 mM/kg CsCl, rapid onset of marked depression of ventricular rhythm (VR) occurred. Note that the sinus rate (SR) remained unchanged. The HBE records atrial activity synchronous with each p wave.
systolic and diastolic pressure rose slightly (5% to 20%) after the administration of CsCl, the sinus slowing may have been in part a response to activation of baroreceptors. There was always alteration of the T wave, often the appearance of a new peak late in the T wave or new wave following it (like a U wave), and a prolongation of the "QU" interval measured from the onset of the QRS to the termination of the slow waves.

When measured at a constant rate in eight animals, the QT interval was prolonged as a QU interval by an average of 55 ± 24% (SD). At a dose of 1 mM/kg CsCl, there was no indication of conduction delay either in change of QRS duration or in ventricular electrograms. However, at higher doses, prolongation of the duration of the QRS complex could be observed transiently within the first minutes when the peak serum levels of cesium were attained.

We administered 1 to 2 mM/kg CsCl intravenously to 12 animals with heart block. Within 1 min after the drug was dispensed we invariably noted a decline in normal ventricular automaticity as we did with the lower doses (figure 1). Within 3 min after injection of CsCl, ventricular paced beats at rates less than 60 beats/min were followed by one or more ventricular ectopic beats. The asystolic period before the inducing ventricular beat was critically related to the ensuing arrhythmia. A typical example is demonstrated in figure 3. In this experiment, ventricular pacing rates faster than 20 beats/min inhibited the rhythm disorder. After cessation of pacing at various rates for 2 min, a variable asystolic interval preceded the first escape ventricular complex depending on the prior paced (overdrive) rate. In Figure 3, B, a regular bigeminy with a coupling interval of 450 msec emerged. At progressively longer asystolic intervals (figure 3, C and D), typical ventricular trigeminy and quadrigeminy resulted. In figure 3, E, with the preceding asystolic period of 8.2 sec, a short run of ventricular tachycardia at a rate of 180 beats/min was observed; also, note the progressively changing QRS complexes.

The rates at which the arrhythmia disappeared and reappeared were variable among different animals and in the same animal with time. At a dose of 1 mM/kg the arrhythmias were transient, occurring in the first few minutes of administration. Therefore, a steady state did not occur and precise characterization of the relationship of the arrhythmia to heart rate was difficult.

In the animals with underlying slow ventricular rates because of heart block, the arrhythmogenic effects may last as long as 15 to 20 min. During this period, repetition of pacing protocols at slow rates demonstrated tachyarrhythmias that could be suppressed by rapid pacing. The arrhythmogenic actions of CsCl were blunted after repetitive application. On completion of the pacing protocol, sufficient time was available to analyze the effects of TTX at a concentration of 1 μg/kg, which did not diminish the amplitude of ventricular electrograms or impair neural activation as assessed by the unchanged rate of supraventricular automaticity and response of atrial rate to vagal stimulation. TTX exerted a strong depressant effect on the occurrence of bradycardia-dependent arrhythmias within 2 min after
injection. After TTX, subsequent CsCl injections failed to initiate any more arrhythmias. In three experiments, TTX administered before the first dose of CsCl prevented the occurrence of arrhythmias. A total dose of 10 to 12 mM/kg CsCl was lethal in our experiments, usually causing a marked fall in left ventricular pressure, conduction disturbances, and ventricular fibrillation.

**Tissue and plasma levels of cesium in vivo.** To correlate in vivo and in vitro concentrations of cesium, we measured the tissue and plasma levels in five dogs. Tissue levels were obtained from atrial muscle to allow for multiple excisions of material without severely damaging the heart. There was a rapid increase in plasma concentration 1 min after injection that rapidly decreased after 5 min, whereas the peak value in the tissue was reached after 10 min followed by a slow decrease. In contrast, the plasma concentration continued to decline rapidly. After 30 min, the heart was excised and additional samples from the ventricular muscle and free-running Purkinje strands were analyzed. Both values were slightly higher than those obtained from the atrium, but were still near the concentration chosen for superfusion of the in vitro preparation (5 mM). The plasma and tissue concentration time-curves are shown in figure 4.

**In vitro experiments.** In voltage clamp experiments, cesium ions have been shown to depress the pacemaker current of cardiac Purkinje fibers and thereby depress diastolic (phase 4) depolarization. This finding was confirmed in our experiments. Figure 5 shows recordings from a spontaneously firing preparation. After addition of cesium (5 mM/l), spontaneous diastolic depolarization of the Purkinje fiber was markedly reduced and the rate was slowed from 44 beats/min to 11 beats/min. Cesium also consistently prolonged action potential duration at a constant heart rate. The apparent positive shift of the transition between phases 4 and 0 was not a consistent finding. In these recordings it may reflect the transformation from latent to true pacemaker in the cell recorded.

The early effects of cesium on transmembrane potentials are illustrated by the recordings shown on figure 6 from a representative experiment. After the addition of cesium (5 mM/l) to the superfusate (figure 6, B), no change in resting potential, action potential amplitude, or V_max could be discerned. However, ac-

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**FIGURE 3.** Effect of rate on spontaneous arrhythmias induced by CsCl (1 mM/kg) in a dog with heart block. Electrocardiographic lead II is recorded. A, Control idioventricular rate was 58 beats/min. After CsCl the rate was markedly depressed and susceptible to overdrive suppression. B-E, After overdrive, the time interval before the first spontaneous beat is indicated below arrows in each panel. Note that with increasing asystolic interval the number of triggered beats increased until in E a burst of ventricular tachycardia ensued.

**FIGURE 4.** Time course of tissue and plasma concentrations of cesium (Cs⁺) after injection of 1 mM/kg CsCl. Note the rapid decline in plasma concentrations after the early peak value compared with the slow changes in tissue concentrations. See text for discussion. PF = Purkinje fiber; VM = ventricular muscle.
tion potential duration increased from 420 to 500 msec, while conduction velocity remained constant as recorded at a faster sweep speed as shown in the right section of figure 6. Note that $V_{\text{max}}$ as represented on the second line from the top is unchanged. Within 20 min after addition to the superfusate, TTX (10^{-8} g/ml) produced a shortening of action potential duration (from 500 to 380 msec), whereas $V_{\text{max}}$ was only slightly diminished (figure 6, C). With cesium (5 mM/l) in the absence of TTX, prolonged action potentials were maintained for as long as 90 min. Some of the cellular electrophysiologic effects observed within 15 min of exposure to cesium and subsequent TTX are summarized in table 1. Our data indicate that cesium prolonged the action potential duration by 36% while other recorded parameters were not significantly altered. Prolongation of the action potential (plateau) usually preceded other alterations of the repolarization phase in Purkinje fibers. The action potential of subendocardial myocardial fibers were also prolonged from 249 ± 36 to 311 ± 47 msec (p < .01).

During continued superfusion with cesium, the rapid repolarization phase (phase 3) of the action potential developed a terminal delay, appearing as an inflection in the course of repolarization as illustrated by the action potentials shown in figure 7, B, compared with the action potentials shown in 7, A. With continued superfusion and lengthening of the cycle length, this delaying inflection became more prominent and assumed the form of a plateau or a positive drift (depolarization) from which action potential upstrokes arose (figure 7, C).

The inflection delaying the course of terminal repolarization always anteceded frank depolarizations. Presumably, the recording of overt afterdepolarizations might depend on proximity of the recording site to the

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**FIGURE 5.** Effect of cesium on normal Purkinje fiber automaticity. A. before cesium, the rate of Purkinje automaticity was 46 beats/min. B. After 5 min of 5 mM cesium, the rate decreased to 11 beats/min associated with depression of the slope of phase 4 depolarization.

**FIGURE 6.** Effect of cesium and TTX on action potentials of canine Purkinje fibers. Top trace is the 0 potential and middle trace the upstroke velocity (dv/dt) in all panels. A. Control. B. After 25 min of superfusion with 5 mM cesium. Action potential duration was markedly prolonged but action potential amplitude, resting potential, $V_{\text{max}}$, and conduction velocity remained unchanged. C. There was marked shortening of the action potential duration 20 min after addition of TTX (10^{-8} g/ml). Stimulation rate, 0.5/sec. Stimuli are indicated by arrows. Vertical calibration factors correspond to action potential and dv/dt recordings, respectively.
BRACHMANN et al.

TABLE 1
Effects of cesium and TTX on action potential parameters of Purkinje fibers (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>AP amplitude (mV)</th>
<th>MDP (mV)</th>
<th>( V_{\text{max}} ) (V/sec)</th>
<th>AP duration (msec)</th>
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<tbody>
<tr>
<td>Control</td>
<td>109.4 ± 5.1</td>
<td>84.1 ± 3.1</td>
<td>465 ± 85</td>
<td>361 ± 42</td>
</tr>
<tr>
<td>Cs 5 mM</td>
<td>107.9 ± 3.4</td>
<td>83.2 ± 2.8</td>
<td>439 ± 82</td>
<td>492 ± 74*</td>
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<td>(30 min)</td>
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<tr>
<td>Cs 5 mM and</td>
<td>102.4 ± 6.2</td>
<td>80.6 ± 4.1</td>
<td>414 ± 97</td>
<td>343 ± 54*</td>
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<tr>
<td>TTX 10^-5 g/ml</td>
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<td>(30 min)</td>
<td></td>
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Results were obtained from eight experiments and with a pacing cycle length of 2000 msec.

AP = action potential; MDP = maximum diastolic potential; Cs = cesium.

Statistical comparisons (two-way analysis of variance): *p < .05 with respect to the control group; **p < .05 with respect to the group superfused with Cs 5 mM alone.

site of initiation of activation in the preparation. Recordings of frank afterdepolarizations are shown in figure 8. Note that the action potentials recorded with a driving rate of 60 beats/min show the delaying inflection in the later third of repolarization but no spontaneous discharges (figure 8, top left), but when the preparation was permitted to fire spontaneously at a slow rate, one of the cells showed a series of afterdepolarizations culminating in spontaneous discharge (figure 8, top right). TTX shortened the action potential, attenuated the delaying inflection at a driving rate of 60 beats/min (figure 8, bottom left), and suppressed the afterdepolarizations and triggered firing at the slow spontaneous rate (figure 8, bottom right). The basic abnormality in the terminal phase of repolarization is also seen in action potentials recorded from the other cell, but afterdepolarizations are less apparent.

The influence of pacing on the phenomenon is illustrated in the recordings shown on figure 9. Figure 9, top left, demonstrates a regular bigeminy with an interposed diastolic interval of 1700 msec in a spontaneously firing preparation. The membrane potential from which the second beat originated was -73 mV, but the maximum diastolic potential was -85 mV. An increase in the asystolic interval to 1850 msec (figure 9, top right) was associated with a greater number of beats linked to the escape complex. Shortening of the cycle length to 1200 msec by regular pacing (figure 9, lower panel) diminished the early afterdepolarizations and the prominence of the delaying inflection, resulting in total suppression of the triggered discharges.

The early afterdepolarizations did not always result in excitation, as demonstrated in figure 10, which shows the recordings from a preparation that was exposed to cesium for 20 min. The fiber exhibited regular bradycardia-dependent early afterdepolarizations causing bursts of spontaneous beats. This was succeeded by an abortive action potential that was followed by decreasing oscillations of the membrane potential until the membrane potential stabilized at -66 mV. After 3.8 sec, an action potential was generated by stimulation, resulting in repolarization to the original membrane potential (-81 mV). Thus, the membrane potential could be relatively stable at another

FIGURE 7. Effect of cesium on terminal repolarization of Purkinje fiber action potentials during pacing at 60 beats/min (A and B) and spontaneous slow rate (C). Top trace, 0 potential; middle trace, upstroke velocity in all panels. After 25 min of superfusion with 5 mM cesium only the action potential duration increased. Note appearance of delaying inflections during the terminal repolarization phase (B, arrows). C, After 40 min of cesium, a spontaneous slow rate (30 beats/min) resulted in a coupled excitation beginning during an apparent second plateau of membrane potential late in the course of repolarization. In this preparation, the two recording sites were 2.5 cm apart near opposite ends of the preparation.
more depolarized level. Further depression of the oscillatory afterpotentials occurred during the recordings of figure 10, D. Again the resting potential stabilized at \(-65 \text{ mV}\) for 7.1 sec until pacing and associated spontaneous beats resumed. Because these oscillations originated at a level of membrane potential more positive than the maximum diastolic potential and they occurred before full repolarization was achieved, we interpreted them as early afterdepolarizations.

**Discussion**

In the present study we used cesium to induce ventricular arrhythmias that are electrocardiographically indistinguishable from the multifurc ventricular tachycardias sometimes induced by certain antiarrhythmic drugs and psychotropic drugs, and that are associated with other conditions such as electrolyte imbalance and marked bradycardia.\(^{21,22}\) The electrocardiographic-clinical entity of torsades de pointes is characterized by markedly prolonged QT (or QU) intervals, multifurc ventricular tachycardia with progressive shifts in the direction of the QRS and T vectors in a sinusoidal pattern, and exacerbation of the ectopy at slower heart rates (bradycardia dependence). The slow waves following the QRS often appear to consist of both abnormal T and U waves. Usually the TU waves are labile from beat to beat, especially with varying cycle lengths. The phenomenon induced by cesium in the whole animal has strikingly similar characteristics. In vitro cesium in concentrations comparable to the tissue levels measured in vivo produced delayed repolarization and early afterdepolarizations that generated triggered firing, especially at slower heart rates. These cellular electrophysiologic effects

**FIGURE 8.** Suppression by TTX of afterdepolarizations and triggered discharges induced by cesium. *Top left.* Action potentials recorded from Purkinje cells 1.8 cm apart driven at 60 beats/min, 55 min after exposure to cesium (5 mM). *Top right.* Recordings made during a slow spontaneous rate, showing afterdepolarizations and triggered activity more prominent in one cell than the other. *Bottom left and bottom right.* Recordings taken under comparable conditions except for exposure to TTX \((10^{-8} \text{ g/ml})\) for 8 min.

**FIGURE 9.** Effect of different rates on transmembrane potentials of Purkinje fibers recorded after 30 min administration of 5 mM cesium. *Upper left.* A bigeminy was observed with a diastolic interval of 1700 msec. Each initial beat was followed regularly by an action potential arising from an early afterdepolarization. *Upper right.* An increase in the diastolic cycle length to 1850 msec led to bursts of ectopic beats each preceded by afterdepolarizations. *Bottom.* After a long asystole, the first paced beat (first arrow) induced an early afterdepolarization and associated response. During repolarization of this beat, the second pacing impulse (second arrow) diminished the afterdepolarization and suppressed further spontaneous activity as pacing (cycle length 1200 msec) continued.
may be the basis for the electrocardiographic changes and arrhythmias observed in intact animals in vivo. It should be noted that the recordings from a few cells in the preparation may not represent all the phenomena occurring in the intact heart. Detailed sampling of ventricular myocardial cells was not performed in these studies. The Purkinje tissues appeared to be involved diffusely, since virtually all sampling sites showed similar phenomena to differing degrees.

Analysis of the tissue levels of cesium demonstrated that these values were in the range of the concentrations in vitro. The difference in the time course of the effects in vivo and in vitro may have been related to rapid initial tissue uptake in vivo that may remain relatively high intracellularly while the plasma concentrations rapidly declined. In contrast, there may have been a continuous uptake of cesium from the superfusate in vitro until a certain intracellular concentration was attained at which the phenomena occurred.

Cesium has been shown to depress potassium currents in Purkinje fibers as well as in other excitable tissues. In Purkinje fibers, the inward rectifying potassium channel is blocked by 20 mM/l cesium. Cesium in low concentrations (1 mM/l) also depressed the pacemaker current, which has been interpreted as a deactivating outward current, \( I_K \), or as an activating inward current, \( i_n \). To account for afterdepolarizations and excitation, it is necessary to consider inward currents. Aconitine, which produces delayed repolarization, early afterdepolarizations, and anomalous (triggered) firing (phenomena resembling those induced by cesium), enhances an inward current activated at \( \sim 60 \text{ mV} \) and blocked by low concentrations of TTX. It has been shown that in normal Purkinje fibers, a noninactivated sodium current flows during the plateau, and this current can be blocked by concentrations of TTX lower than those required to block the excitatory fast sodium current. In light of these observations, we used low concentrations of TTX to provide an indication of the implication of the sodium current in the afterdepolarizations and anomalous excitations caused by cesium. The suppression of afterdepolarizations and abolition of triggered excitation by low concentrations of TTX suggest that the noninactivated sodium current is involved. Cesium has not been shown to enhance an inward current. It may be that the "normal" noninactivated sodium current is sufficient to result in afterdepolarizations and triggered discharges if repolarization is sufficiently delayed and outward currents are blocked. The bradycardia dependence of the afterdepolarizations probably relates to the prolongation of repolarization with longer cycle lengths. Also, at shorter cycle lengths, extracellular potassium concentration increases, resulting in increased potassium conductance, which would partially reverse the effects of cesium.

FIGURE 10. Effect of cesium on transmembrane potentials of Purkinje fibers. A and B, Bradycardia-dependent early afterdepolarization and bursts of spontaneous activity after 20 min of superfusion with 5 mM cesium. C, After 2 min, the second paced action potential (second arrow) elicited an early afterdepolarization leading to brief oscillations of the membrane potential. Afterward the potential remained at this depolarized level. A stimulated action potential (third arrow) introduced after 3.5 sec caused repolarization to the former resting potential. D, After another oscillatory response, the membrane potential persisted for 6 sec at a depolarized level. Another paced beat triggered spontaneous action potentials followed by more complete repolarization.
It was not possible in this study to define precise relationships between cycle length and early afterdepolarizations or spontaneous discharges. The relationships were variable with time and among preparations. However, there was a consistent inverse relationship between the occurrence of triggered firing and the heart rate.

In experimental and clinical studies, bradycardia-dependent arrhythmias have been attributed to reentry. In patients with atrial fibrillation, Langendorf et al. defined a specific "rule of bigeminy" demonstrating bradycardia-dependent increase in frequency of ectopic beats. In patients with bradycardia due to heart block, multifascicular ventricular tachyarrhythmias have been observed that very closely resemble the type described as torsades de pointes. It has been proposed that temporal dispersion of refractoriness is the basis for reentrant mechanisms with bradycardia. However, dispersion of refractoriness cannot be a sole mechanism for the generation de novo of ectopic beats because it requires that an impulse interrupt the refractory period of a beat during the stable rhythm. Therefore, even under conditions of markedly dispersed refractoriness, another mechanism is required for the initial ectopic beat(s) that might in turn result in subsequent reentrant beats. In our studies, dispersion of refractoriness and reentry could have come into play after one or more automatic beats. Repolarization was abnormally prolonged and probably abnormally heterogeneous. However, dispersion of refractoriness was not quantified. We propose that the arrhythmias induced by cesium have as their initiating mechanism, triggered firing due to early afterdepolarizations. It is possible that reentry is also operative because heterogeneous delay of repolarization might produce dispersion of refractoriness. An arrhythmia resembling torsades de pointes has been observed in ischemic dog hearts in which mapping of activation has suggested two competing activation sequences, presumably representing two reentrant circuits.

Reports of patients treated with certain antiarrhythmic drugs and psychotropic drugs have revealed a significant incidence of tachyarrhythmias and sudden death. This was related to marked prolongation of the QT (or QU) interval, which might facilitate reentry by inhomogeneous repolarization. Catecholamine infusion and atrial pacing to shorten the QT interval have been useful in suppressing these arrhythmias. In general, the drugs that have been shown to produce these multifascicular ventricular tachyarrhythmias have been those that prolong the QT interval and delay repolarization within normal Purkinje and myocardial fibers.

Drugs that facilitate repolarization and shorten the QT interval, such as lidocaine, generally have not been implicated in this phenomenon. Perhaps certain individuals are especially sensitive to the effects of certain drugs to block outward currents and delay repolarization, and as a result these individuals are susceptible to the generation of tachyarrhythmias. Other factors operating in certain individuals, such as myocardial hypertrophy, may also potentiate the effects of drugs that delay repolarization. It has been shown recently that hypertrophied myocardium in rats is prone to the development of early and delayed afterdepolarizations under certain conditions. The occurrence of torsades de pointes with hypokalemia or hypocalcemia fits with the proposed mechanisms, since potassium conductance would be expected to be decreased in those conditions. Since torsades de pointes can occur in the absence of drugs or electrolyte alterations under conditions of marked bradycardia, it is possible that the delay of repolarization attendant on bradycardia alone sometimes results in early afterdepolarizations and automatic firing.

The hypothesis that torsades de pointes associated with long QT intervals is based on the cellular electrophysiologic phenomena of early afterdepolarizations and triggered firing, rests for the most part on the similarity of the phenomena produced by cesium in vivo in dogs to the clinical entity: the prolongation of the QT interval, the appearance of U waves, the variability of the T and U waves, the undulating pattern of the multifascicular tachycardia, and the bradycardia dependence. Further support for the hypothesis is provided by the observation that the major metabolite of procainamide, N-acetyl procainamide, which attains significant concentrations in humans (especially in individuals who are rapid acetylators), has been shown to produce early afterdepolarizations associated with markedly delayed repolarization in Purkinje fibers.

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