Cesium chloride–induced long QT syndrome: demonstration of afterdepolarizations and triggered activity in vivo

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ABSTRACT The identification of afterdepolarizations and their relationship to arrhythmias in vivo is not available. Experiments were undertaken to determine whether afterdepolarizations could be detected in monophasic action potentials (MAPs) recorded in vivo and whether they were related to arrhythmias in an intact canine preparation of the long QT syndrome. Isolated cardiac tissues from six dogs were studied to validate the technique. In simultaneous MAP and transmembrane recordings, afterdepolarizations induced with barium (early) or acetylstrophanthidin (delayed) were detected in MAPs when present in microelectrode recordings. MAPs were then recorded in situ in eight dogs with cesium chloride–induced long QT syndrome associated with ventricular arrhythmias. Afterdepolarizations were identified in each of the dogs and were similar to early afterdepolarizations identified in vitro; they occurred during phase 3 and were attenuated during overdrive pacing. The afterdepolarizations were closely related to arrhythmias: (1) afterdepolarizations always preceded ventricular arrhythmias, (2) the coupling intervals (CI) of the afterdepolarizations (AD) and the ventricular premature beats (VPB) were nearly identical (VPB CI = 1.06 AD CI − 10.24; r² = .87), (3) the take-off potentials of the ventricular premature beats were nearly identical to the amplitude of the afterdepolarizations (take-off potential = 0.98 afterdepolarization amplitude + 0.46, r² = .87), and (4) afterdepolarizations and ventricular arrhythmias resolved concurrently during overdrive pacing and with time. Thus, a new catheter technique has been validated and has been used to directly identify afterdepolarizations and triggered activity in vivo.


CURRENT electrophysiologic techniques do not allow for the unequivocal identification of arrhythmia mechanisms in vivo. The characteristic response of an arrhythmia to pacing has been used to differentiate reentrant rhythms from enhanced automaticity; however, direct proof of a reentrant mechanism in vivo is available only in the case of reciprocating tachycardia using an accessory pathway. At present no technique is available to distinguish triggered activity from other arrhythmic mechanisms. Although there have been reports of rhythm disturbances that fulfill the criteria for triggered activity, conclusive identification of afterdepolarizations or their relationship to atrial or ventricular arrhythmias in vivo is not available. The mechanisms of the tachyarrhythmias associated with a prolonged QT is one example. That programmed electrical stimulation does not lead to reproducibly inducible tachycardia suggests that the arrhythmias may not be due to reentry. Recent data obtained in vitro indicates that the ventricular ectopic activity that develops in this situation may be a result of triggered activity. Early afterdepolarizations and triggered activity have been identified in isolated canine ventricular muscle and Purkinje fibers after exposure to agents or conditions known to cause ventricular tachyarrhythmias, torsade de pointes, and a long QT interval in animal preparations. However, the conclusive identification of afterdepolarizations and triggered activity in vivo in this or other settings is not available.

Monophasic action potentials (MAPs) can be re-
corded in situ from the beating canine left ventricle with a contact or suction electrode. The time course of repolarization of MAPs has been shown to correlate closely with that of simultaneous transmembrane action potentials under a variety of conditions. MAPs arise as a result of passive current flow from one endocardial cell to apparent depolarization of the MAP and therefore the MAP should have been used to detect membrane phenomena such as afterdepolarizations. The present article describes a series of studies designed to document afterdepolarizations and triggered activity in vivo. The detection of afterdepolarizations in MAPs was first validated in vitro and the characteristics of the MAPs and afterdepolarizations that developed after the administration of cesium chloride were then determined in a canine preparation with a prolonged QT interval and torsade de pointes. The behavior of the afterdepolarizations and ventricular ectopic activity was compared during ventricular pacing to provide additional evidence of triggered activity in vivo.

Methods

Experiments in vitro. To validate that afterdepolarizations can be detected in MAPs experiments were performed on tissues removed from six adult mongrel dogs weighing between 8 and 16 kg. The animals were anesthetized with intravenous sodium pentobarbital (30 mg/kg), their chests were opened via a left lateral thoracotomy, and their hearts were removed. Endocardial or epicardial tissue samples 1 to 2 mm thick, 2 cm wide, and 2 to 3 cm long were removed and placed in a 100 ml tissue bath filled with oxygenated Tyrode's solution (standard unless otherwise stated). The methods used have been described previously. The tissues were paced at a basic cycle length of 1000 msec with a bipolar stimulating electrode consisting of two Teflon-coated silver wires positioned at one end of the tissue. Constant-current square-wave pulses of 2 msec duration and twice diastolic threshold intensity were used.

MAP and transmembrane potential recordings. MAPs were recorded with a silver-silver chloride electrode. The distal tip (1 mm in diameter) was used as the recording electrode and a distal bath ground was used as the reference electrode. In addition, with the use of standard 3M potassium-filled microelectrodes, transmembrane action potentials were recorded from Purkinje fibers or superficial muscle cell layers within 4 mm of the contact electrode. Both MAP and microelectrode recordings were displayed on a memory oscilloscope (Tektronix) and recorded on an electrostatic paper recorder (Gould) at paper speeds of 25 to 250 mm/sec.

Afterdepolarization experiments. In tissues from three animals, early afterdepolarizations were induced with 10^{-8} M barium chloride in standard Tyrode's solution. Epicardial tissue preparations were used to ensure homogeneity of local repolarization in the baseline state. Simultaneous MAP and transmembrane recordings were made. A stable MAP and a continuous, stable microelectrode impalement were required for the data to be accepted.

Delayed afterdepolarizations were induced with acetylstryphanthidin (5 x 10^{-8} g/liter) in endocardial tissues taken from the left ventricles of three different animals. For these experiments, the Tyrode solution was altered: The concentration of K+ was increased to 4 meq/liter and that of Ca^{2+} to 2.5 meq/liter. The contact electrode was placed either over free-running Purkinje fibers or muscle. Transmembrane recordings were also made from Purkinje or muscle cells.

Once afterdepolarizations were induced with acetylstryphanthidin, the tissues were paced at the following cycle lengths: 1000, 800, 600, 500, 400, and 300 msec. The changes induced by pacing in the MAP and transmembrane recordings were compared. Specifically, amplitude changes of the afterdepolarizations and coupling intervals were determined in each case for both recording methods. Afterdepolarization amplitude was defined as the difference in voltage between the peak amplitude and the most negative membrane voltage noted preceding their onset. Afterdepolarization coupling interval was defined as the time from the onset of the action potential to the time of peak amplitude. Amplitude and coupling interval were measured to the nearest millivolt and 5 msec with a Hewlett-Packard 9825A computer and 9864 manual digitizer.

Experiments in vivo. Experiments were performed on eight mongrel dogs of both sexes that ranged in weight from 10 to 24 kg. Animals were anesthetized with pentobarbital (30 mg/kg) and ventilated with room air with the use of a constant-volume ventilator. Catheters were placed in the jugular or femoral vein for infusion of drugs. After a median sternotomy, the pericardium was opened and the heart exposed.

Bipolar pacing leads consisting of two Teflon-coated silver wires exposed at the tip were placed in the right atrial appendage and in the left and right ventricle. Pacing was performed at twice diastolic threshold with a programmed stimulator and a constant-current source (Bloom). MAPs were recorded from the left ventricular epicardium in all eight animals and were simultaneously recorded from the left ventricular endocardium and epicardium in four animals. A bipolar catheter consisting of a silver-silver chloride distal electrode and a reference lead 5 mm away was advanced into the left ventricular cavity via the left carotid artery and positioned against the anterior-apical endocardial surface. Epicardial recordings were obtained from the left anterior ventricular surface by a similar catheter arrangement modified to allow for stable recordings from the beating heart in situ. The MAP signals were amplified and filtered at a frequency of 0.1 to 10 kHz. The surface electrocardiographic lead, amplified MAP signals, and left and right ventricular local bipolar electrograms were simultaneously displayed on an oscilloscope (Tektronix) and recorded on an electrostatic paper recorder (Gould). After this preparation was completed, baseline recordings were obtained sequentially from five to 10 epicardial sites at the sinus heart rate and during pacing at several other more rapid rates. The duration, amplitude, and morphology of the MAPs were noted and the absence of afterdepolarizations was verified. The epicardial probe was then placed in a position that allowed for long-term stable recording from the left ventricular surface.

Cesium chloride (1 mM/kg) was administered as an intravenous bolus over 15 sec via a central venous catheter positioned in the femoral or jugular vein. When either a prolonged QT interval, afterdepolarizations in the MAP, or ventricular ectopic activity developed and reached a steady state, atrial and ventricular pacing was performed at several cycle lengths that were shorter than the sinus cycle length. The behavior of the ventricu-
lar ectopic activity and changes in the MAP after 8 to 10 paced beats were analyzed.

Phases 0 to 4 of the MAP were defined in the same way as the phases of a conventional transmembrane action potential. The amplitude of the MAP was defined as the potential difference between phase 2 and phase 4 of the MAP. The duration of the MAP was determined at 90% repolarization. Either delay in repolarization or true depolarizations occurring during phase 2 or phase 3 of the MAP were termed MAP afterdepolarizations. The coupling interval was defined as the interval between phase 0 of the MAP and the peak or shoulder of the afterdepolarization that developed. The amplitude of the MAP afterdepolarizations were defined and determined in a manner analogous to that described for early afterdepolarizations in conventional transmembrane recordings. Only data from recordings considered stable were included in the pooled data. The first criteria for stability was a stable resting potential. In those cases in which ectopic activity arose from the afterdepolarizations, stable resting potentials for each ectopic beat and for the first beat after cessation of the tachycardia, although different from each other, were required. Second, a stable relationship between the amplitudes of phase 2 and phase 0 was required.

The QT interval was defined as the time between the first deviation from an isoelectric PR interval until the last deviation from baseline before the isoelectric UP interval.

**Controls for changes in MAP induced by motion.** To determine whether an increase in contractility and an accentuation of regional wall motion might lead to motion-induced changes in the repolarization phase, epinephrine was infused in six dogs. These animals were anesthetized and prepared in the same manner as the dogs that were to receive cesium chloride. In addition, two pairs of ultrasonic crystals were implanted in the midwall of the left ventricle parallel to the minor axis of the heart. One pair was positioned in the anterior and another in the posterior wall of the left ventricle. Left ventricular pressure and dP/dT were monitored with a catheter/tipped pressure transducer (Millar). In each animal, MAPs were sequentially recorded from 10 to 20 ventricular sites during atrial overdrive pacing at baseline. Epinephrine was then infused at increasing infusion rates intravenously and the dose that led to a maximal hemodynamic response was determined. MAPs were then recorded again from 10 to 20 ventricular sites during atrial overdrive pacing and their characteristics were noted. In each experiment, changes occurred in the MAP, but were limited to a decrease in MAP duration. These changes were not statistically significant. An example is presented in figure 1. Stable recordings were consistently acquired in spite of an increase in heart rate, regional wall motion, blood pressure, and contractility. Furthermore, neither discontinuity in the repolarization phase nor afterdepolarizations were noted at any site in any animal at baseline or after epinephrine.

These results suggest that wall motion, per se, does not lead to abnormalities in repolarization of MAPs. Nevertheless, instability of the MAP recording (as well as of intracellular recordings for that matter) may exist. To avoid artifacts and ensure stable recordings in the present series of experiments, the following were carefully considered when designing the experimental protocol: (1) Control recordings from several sites were made in each animal. (2) A stable baseline recording position was identified in each animal, only after which cesium chloride was administered. (3) The current experimental preparation was used because the genesis of arhythmias in vivo and afterdepolarizations and triggered activity in vitro have been shown to occur in a matter of minutes. Although prolonged MAP recordings have not been associated with abnormalities in repolarization, this feature of the preparation made it particularly easy to maintain stable, continuous recordings throughout the experimental protocol. (4) Several experiments were performed while monitoring left ventricular pressure and regional wall motion.

**Statistical methods.** Pooled data are expressed as mean ± SD. Comparison of means was performed with the use of a paired t test. Correlations between variables was determined by linear regression. A p value less than or equal to .05 was considered indicative of a significant difference and an r² value greater than or equal to .70 was considered to indicate a significant positive correlation between variables.

**Results**

*Validation in vitro.* In tissue samples from six dogs in which simultaneous MAPs and conventional trans-
membrane action potentials were recorded, afterdepolarizations were induced with barium chloride (early) or acetylstrophanthidin (delayed).

Delayed afterdepolarizations and triggered activity were induced in endocardial tissue preparations containing Purkinje fibers taken from the left ventricle. Delayed afterdepolarizations were noted in Purkinje fibers but not in adjacent ventricular muscle under the conditions of the tissue bath. Triggered activity arose from the Purkinje cells and was able to capture neighboring muscle cells in all cases. Shown in figure 2, A are analog records from one tissue before and after

FIGURE 2. Afterdepolarizations that developed in an endocardial preparation exposed to acetylstrophanthidin (5 × 10⁻⁶ g/liter). A, Analog records of simultaneous monophasic and transmembrane action potentials before and after acetylstrophanthidin (ACS). Note that the delayed afterdepolarization present in the transmembrane recording after acetylstrophanthidin is accurately detected by the contact electrode (arrows). B, An analog recording from the same tissue sample demonstrating the effect of pacing on the afterdepolarizations of the MAP and transmembrane recordings. An increase in the pacing rate leads to an increase in the prominence of the afterdepolarizations in both the MAP and TAP recordings (arrows). Note also that the characteristic changes in phase 4 during pacing are apparent in the MAP as well. C, Results from a different tissue sample in which pacing-induced changes in afterdepolarizations in simultaneous monophasic and transmembrane recordings were compared. Again, although of lower amplitude, delayed afterdepolarizations detected in MAPs behaved the way afterdepolarizations in conventional recordings did during pacing experiments. This tissue was paced for 10 beats at various cycle lengths and afterdepolarization amplitude in transmembrane and monophasic recordings were compared. Afterdepolarization amplitude in both types of recordings increased at decreasing pacing cycle lengths and reached a maximal amplitude at a basic cycle length of 500 msec. At shorter pacing cycle lengths, afterdepolarizations amplitude decreased in both records. The left and right amplitude scales refer to the transmembrane and monophasic recordings, respectively. TAP = transmembrane action potential.
exposure to acetylstrophantidin; certain features of the MAPs are well shown in the baseline recordings. The time course and configuration of the repolarization phase of the transmembrane action potential were similar to those of the repolarization phase of the MAP. The amplitude of the MAP, on the other hand, was lower than that of the corresponding transmembrane action potential. At baseline, afterdepolarizations were not present in either the transmembrane or monophasic recordings. After exposure to acetylstrophantidin, afterdepolarizations developed. Afterdepolarizations and changes in phase 4 depolarization were noted in MAPs that were recorded from Purkinje fibers when present in simultaneous microelectrode recordings. In addition, during overdrive pacing at different cycle lengths, changes in the amplitude of the first delayed afterdepolarization in the transmembrane recordings were accurately detected by the MAP. Figure 2, B shows a continuous analog recording that demonstrates these effects. As illustrated in this figure, shorter pacing cycle lengths led to more prominent afterdepolarizations in both the monophasic and transmembrane recordings. Figure 2, C demonstrates the same findings in a different tissue sample. Although of different absolute amplitude, changes in afterdepolarization amplitude in the transmembrane recordings were accurately detected in the MAPs. In this tissue, peak afterdepolarization amplitude in both transmembrane potentials and MAPs occurred at a pacing cycle length of 500 msec.

Early afterdepolarizations induced in epicardial preparations with barium chloride (10^-7 M) were also detected in MAPs (figure 3). In this experiment the transmembrane action potential was recorded within 2 mm of the contact electrode. The afterdepolarization present in the transmembrane action potential was accurately recorded in the MAP and the phase 4 depolarization was also detected. As with delayed afterdepolarizations, changes in the amplitude of early afterdepolarizations associated with changes in coupling interval were also accurately reflected in the MAP. Specifically, longer coupling intervals led to early afterdepolarization of greater amplitude.

Characteristics of the MAP: changes induced by cesium chloride in vivo. Baseline MAP recordings showed a rapid upstroke, a plateau, and a smooth, continuous repolarization phase. Epicardial MAP amplitudes ranged from 12.0 to 49.2 mV (mean 32.4 ± 8.6 mV), while endocardial MAP amplitudes ranged from 6.5 to 21.4 mV (mean ± SD = 12.7 ± 4.4 mV). No delayed repolarization or afterdepolarizations during either phase 2 or 3 were noted in baseline recordings. After the administration of cesium chloride, a prolongation of phase 2 and the development of afterdepolarizations occurred. Figure 4 is an analog recording from an experiment in which simultaneous endocardial and epicardial MAPs were recorded. Baseline recordings are shown in panel A and recordings 15 sec after the administration of cesium chloride are shown in panel

![Map](https://example.com/map.png)

**FIGURE 3.** Early afterdepolarizations (small arrows) were induced in an epicardial preparation by barium chloride (10^-7 M). The afterdepolarizations were present, in both the transmembrane action potentials (TAPs) and MAPs for the first beat but not the second beat. Phase 4 depolarization present in the transmembrane potential was also accurately detected by the MAP (large arrows).

![Map](https://example.com/map.png)

**FIGURE 4.** A. Baseline MAPs recorded simultaneously from endocardium and epicardium. A rapid upstroke, a plateau, and smooth and continuous repolarization phase are noted. Note that relatively little dispersion of onset of activity or of repolarization is present in the baseline state. B, MAPs recorded from the same positions approximately 15 sec after the administration of cesium chloride demonstrate several changes. Prolongation of the plateau is noted in the epicardial trace, while an afterdepolarization (arrow) interrupts the repolarization phase of the endocardial trace. A significant dispersion in repolarization arises (dotted line) after the administration of cesium.
B. Very soon after the administration of cesium, a prolongation of phase 2 occurred in the epicardial recording while an afterdepolarization developed in the endocardial recording. These initial changes were seen in all of the experiments. Subsequently, afterdepolarizations were the predominant finding. The amplitude of the afterdepolarizations ranged from 0.7 to 15.6 mV (mean 5.0 ± 4.2 mV) in the epicardial recordings and from 0.5 to 4.6 mV (mean 2.7 ± 1.3 mV) in the endocardial recordings. The afterdepolarizations were seen with equal frequency and relative prominence on both endocardial and epicardial recordings. In addition, prominent TU waves were occasionally noted in the local bipolar electrograms and they correlated in time with the afterdepolarizations. The QTU interval prolonged concurrently with the development of the MAP changes (QTU, before infusion 360.3 ± 30.5 msec; QTU, after infusion 453.0 ± 31.2 msec). The QTU interval correlated with the MAP duration before as well as after the cesium-induced changes. These data and their regression are shown in figure 5.

When the cesium effect had reached a steady state the afterdepolarizations that developed responded in a characteristic way to overdrive pacing. Pacing at short cycle length led to the attenuation of afterdepolarizations. Figure 6 is an example of analog recordings from one such experiment. At each shorter pacing cycle length, the amplitude of the afterdepolarizations and the area under the afterdepolarization progressively diminished. At the shortest cycle length (in this case, 300 msec), the afterdepolarizations are nearly abolished. This same behavior was noted in each of the experiments. Figure 7 presents the sumary data for the eight experiments. In each case, pacing at shorter cycle lengths led to attenuation of the afterdepolarizations.

The afterdepolarizations that developed were relatively short-lived. They became less prominent over time and finally disappeared after 10 to 15 min. Of interest is that in all cases the time course of the disappearance of the MAP afterdepolarizations followed that of normalization of the QTU interval.

**Relationship of the afterdepolarizations to ventricular ectopy.** After the administration of cesium chloride, ventricular ectopy developed in seven of eight experiments. In the animal that did not develop ventricular arrhythmias, sinus arrest, atrioventricular block, and a narrow, junctional tachycardia developed after administration of cesium. Ventricular arrhythmias were spontaneous in all cases. Four animals developed sustained ventricular tachycardia (at least 30 consecutive sec of tachycardia) and three animals developed torsade de pointes (figure 8). Ventricular fibrillation re-
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quiring cardioversion occurred in one dog. Bigeminy or short salvos of nonsustained ventricular tachycardia were noted in all but the one experiment.

MAP afterdepolarizations were associated with the development of ventricular ectopy in each case. In all experiments, there was a progressive increase in afterdepolarization amplitude during the first minute after the administration of the cesium chloride. In no case did ventricular ectopy develop without the prior development of the afterdepolarizations. Figure 9 presents typical analog tracings recorded in an animal approximately 1 min after the administration of cesium chloride. An afterdepolarization developed in phase 3 of the MAP, it became progressively larger, and was associated with the development of an ectopic ventricular beat. The coupling interval of the ventricular ectopic beat was very similar to that of the afterdepolarization in this case. This relationship was present in each experiment. Figure 10 presents the summary data relating the coupling intervals of the ectopic beats to the afterdepolarization coupling intervals. These variables are closely related and the coupling intervals of the afterdepolarizations are nearly identical to those of the corresponding ectopic beats.

Moreover, the take-off potential for each ectopic beat was related to the afterdepolarization amplitude in

FIGURE 6. The response of the afterdepolarizations to overdrive pacing. A to D, Analog epicardial recordings from an experiment in which afterdepolarizations developed after the administration of cesium chloride. Atrial overdrive pacing led to progressive attenuation of the afterdepolarizations (arrow) at shorter cycle lengths.

FIGURE 7. The effect of overdrive pacing at various cycle lengths on the amplitude of the afterdepolarization (A) as well as the area under the afterdepolarization (B) for each experiment. Both of these measured variables decreased at progressively shorter pacing cycle lengths in each experiment. (Each line represents a separate experiment).
each experiment; that is, the take-off potential in every case approximated the baseline resting potential plus the afterdepolarization amplitude. Figure 11 illustrates analog recordings in which endocardial and epicardial MAPs were recorded simultaneously with right and left ventricular electrograms and a surface electrocardiographic lead. Salvos of nonsustained ventricular tachycardia developed in this animal approximately 45 sec after the administration of cesium. The MAP of the terminal beat in each salvo was associated with an afterdepolarization. The take-off potentials of the last ectopic beat in each salvo were nearly the same and approximate the amplitude of the subthreshold afterdepolarizations. Also, the resting potential from which the first beat after the termination of each salvo arose was relatively constant, demonstrating a stable recording throughout. In addition, the afterdepolarizations present in the epicardial and endocardial tracings, although of different absolute amplitudes, were proportionally the same relative to the MAP amplitude. The close relationship of the take-off potential of the ectopy and the amplitude of the afterdepolarization is summarized in figure 12.

Termination of ventricular ectopy was also related to the properties of the afterdepolarizations. The afterdepolarizations became attenuated during atrial or ventricular overdrive pacing at short cycle lengths (figures 6 and 7) as well as after 10 to 15 min elapsed time following the administration of cesium chloride. Ventricular ectopy was also suppressed during overdrive pacing. In addition, all spontaneous ventricular ectopy ceased as the afterdepolarizations became attenuated with elapsed time (after the initial injection). Thus, the genesis and termination of the ventricular ectopic beats were correlated with the presence or absence of MAP afterdepolarizations.

Discussion

In this study, a new technique for recording MAPs was validated, its sensitivity to record membrane phenomena was determined in vitro, and its application for recording these membrane phenomena was demon-
The major finding in this study is that afterdepolarizations and triggered activity occur in vivo and that they underly the genesis of ventricular arrhythmias and torsade de pointes in an animal preparation of the long QT syndrome. In addition, it was shown that the afterdepolarizations and ventricular ectopy that developed behaved in a manner predicted from studies in vitro in isolated tissue preparations exposed to cesium chloride.7. 8 MAPs can be recorded from cardiac tissue that has been injured by suction or pressure and are thought to result from current flow from immediately adjacent normal cells that remain electrically coupled to injured tissue beneath the suction or contact electrode.9-13 The time course of the plateau and repolarization phases of the MAP have been shown to correlate with that of neighboring action potentials.9, 13 One might predict that other perturbations in the transmembrane voltage either during phase 2 or 3 (early afterdepolarizations) or during phase 4 (delayed afterdepolarizations, enhanced phase 4 depolarization) should also be detectable. This, in fact, was the case in our experiments in vitro. Membrane effects that perturbed phase 2 or 3 or that occurred during phase 4 were accurately detected in MAPs recorded with the contact electrode. Although the absolute voltage of the MAPs differed significantly from that of transmembrane action potentials, enhanced phase 4 depolarization as well as early and delayed afterdepolarizations present in transmembrane action potentials were also recorded in MAPs in vitro (figures 2 and 3).

After the administration of cesium chloride in vivo, afterdepolarizations were also noted during phase 3 of the MAP. We have not proven that these afterdepolarizations recorded in the MAPs in our animal preparation in vivo represent the same phenomenon as that represented by afterdepolarizations noted in conventional transmembrane action potentials recorded in isolated preparations exposed to cesium chloride. Our data, however, do suggest that this may be the case. MAPs and the afterdepolarizations that develop in response to cesium chloride share many characteristics with conventional action potentials recorded from isolated preparations exposed to cesium chloride.7, 8 Cesium chloride-induced prolongation of the MAP in vivo (figure 4) is similar to the phenomenon described for transmembrane recordings under similar conditions (figure 3). In addition, the time course and morphology of the afterdepolarizations noted in MAPs are similar to those described for early afterdepolarizations of the type that develop at high resting membrane potentials.8 Furthermore, the pacing-induced changes

FIGURE 10. The coupling intervals of the afterdepolarizations (AD CI) and the premature ventricular beats (PVB CI) were strongly correlated and nearly identical. The graph is arranged similar to that of figure 5.

\[
y = -10.24 + 1.06 x \\
\text{r}^2 = 0.87 \\
n = 145
\]
in the afterdepolarizations (figures 6 and 7) that were noted in our experiments are similar to those described for early afterdepolarizations identified in vivo. It thus seems highly probable that the phenomena we have recorded in vivo are the same as those identified in conventional transmembrane recordings in isolated preparations.

The afterdepolarizations seemed to play an important role in the genesis of the ventricular ectopic activity that arose. The development of afterdepolarizations preceded the development of arrhythmias in all cases. In addition, in several dogs, a clear progression in afterdepolarization amplitude before a spontaneous premature beat was noted, thereby suggesting that the premature beat resulted from a threshold response (figure 9). Furthermore, the coupling intervals of the afterdepolarizations were closely related to and nearly the same as the coupling intervals of the associated ventricular premature beats (figures 9 and 10). In addition, the take-off potential of the premature beats in the MAP recording was related to the afterdepolarization amplitude (figures 11 and 12). Finally, both the ectopy and the afterdepolarizations resolved concurrently during overdrive pacing or with time; the animals returned to a near-baseline electrophysiologic condition 5 to 10 min after the cesium infusion. Thus, a clear relationship between the MAP afterdepolarizations and the ventricular ectopy that developed was present in this in vivo preparation. It should be noted that the arrhythmias that arose in vivo were considerably faster than those described in vitro and that the initial coupling intervals of the ectopic beats were shorter. While the exact reason for this difference is unknown, it is likely related to sympathetic tone that is present in vivo.

The mechanism underlying the development of the afterdepolarizations that occur after the administration of cesium chloride is unknown. Early afterdepolarizations develop in vitro in ventricular muscle or Purkinje fibers exposed to agents or conditions that favor prolonged repolarization. Their genesis is thought to be due in part to cesium-induced depression of potassium currents. However, definite evidence for the presence of an altered ionic current leading to the genesis of early afterdepolarizations is not available. Furthermore, the possibility that some early afterdepolarizations might represent an electrotonic membrane phenomenon has not been ruled out in our experiments nor in most experiments in vitro. In fact, data from our studies suggest that electrotonic phenomena may have been involved in the genesis of some afterdepolarizations. Figure 4 is taken from an experiment in which simultaneous endocardial and epicardial MAPs were recorded. Cesium chloride induced a similar prolongation of the MAP duration within 15 sec in both tracings. However, the prolongation found in the epicardial recording was due to a prolongation of phase 2, while that in the endocardial tracing was due to the development of an afterdepolarization with relatively little change in phase 2. This suggests that the afterdepolarizations found in this case may have been due to electrotonic phenomena resulting from dispersion of repolarization. In addition, the ectopy that developed could have arisen via current flow between cells with prolonged and shortened repolarization phases by a mechanism similar to that described for ischemia.

The possibility that the afterdepolarizations arose as a result of ventricular wall motion or an unstable catheter position seems unlikely. First, control recordings under baseline conditions as well as after an epinephrine-induced increased contractile state (over 100 recording positions) failed to show similar changes dur-
ing phase 2 or 3 (figure 1). If these recordings of afterdepolarizations in vivo were due to motion-induced changes in contact pressure, they should have been accentuated under these conditions. Second, simultaneous endocardial and epicardial tracings were made after administration of cesium chloride and afterdepolarizations of the same relative magnitude and polarity were demonstrated in both MAP recordings (figure 11). If wall motion affecting the electrode-myocardial interface were the cause of the afterdepolarizations (i.e., during contraction or filling) one might predict humps of opposite polarity in the two recordings; i.e., the ventricular wall is always moving toward one of the catheters thereby potentially increasing contact pressure while moving away from the other. Third, if motion underlied their genesis, one would not expect the close correlation between the MAP duration and the QTU interval (figure 5), or the close relationship between the afterdepolarizations and the ventricular ectopic activity documented in our experiments (figures 9 to 12). Fourth, in three experiments in which simultaneous left ventricular pressure was monitored, and in two experiments in which regional wall motion was measured with ultrasonic crystals, no relationship was found between the afterdepolarizations and changes in the hemodynamic parameters. Fifth, the afterdepolarizations became attenuated during rapid overdrive pacing (figures 6 and 7). If they resulted from instability due to ventricular wall motion, one would expect them to be accentuated by pacing at rapid rates. Finally, afterdepolarizations such as these have been noted in vitro during simultaneous MAP and transmembrane recordings under similar conditions, and that the MAP catheter can clearly detect these membrane phenomena has been validated in vitro (figures 2 and 3). Thus, the evidence is in favor of the fact that the afterdepolarizations recorded in our experiments are representative of similar phenomena present in nearby myocardial cell action potentials.

The findings in this study are clinically relevant. The long QT syndrome, acquired or congenital, has been associated with ventricular ectopic activity and torsade de pointes. Although assumed to be due to triggered activity, the mechanism of these arrhythmias in vivo have not been defined. The present studies provide direct evidence linking afterdepolarizations, the characteristics of which are similar to early afterdepolarizations defined in vitro, with ventricular ectopy in this animal preparation of the long QT syndrome. We have further defined a mechanism by which conventional management of these patients, such as overdrive pacing, may exert a beneficial effect.
findings in this study may be relevant to the long QT syndrome in man is further suggested by the demonstration of similar afterdepolarizations in right ventricular MAPs in patients with acquired or congenital long QT syndrome and severe ventricular arrhythmias. Thus, recording MAPs in patients with the long QT syndrome may help to identify those at risk for the development of tachyarrhythmias as well as provide an assay in the electrophysiology laboratory against which drugs, pacemakers, or other therapeutic interventions can be measured.

We thank Ralph Iannuzzi, William Moore and Chuck Prood for their technical assistance and Bejay Moore for typing the manuscript.

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Cesium chloride-induced long QT syndrome: demonstration of afterdepolarizations and triggered activity in vivo.
J H Levine, J F Spear, T Guarnieri, M L Weisfeldt, C D de Langen, L C Becker and E N Moore

_Circulation_. 1985;72:1092-1103
doi: 10.1161/01.CIR.72.5.1092

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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