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Triggered Activity as a Cause of Bigeminy

ROBERT S. KIEVAL, BA,* NANCY J. JOHNSON, MD, MICHAEL R. ROSEN, MD, FACC

New York, New York

Standard microelectrode techniques were used to study bigeminal rhythms occurring during otherwise stable triggered activity in ouabain-toxic canine Purkinje fibers. The basis for the bigeminy appeared to be an alternans phenomenon in the delayed afterdepolarizations that induced the triggered activity, as well as in the maximal diastolic potential. The occurrence of bigeminy, previously thought to result from reentry, from single delayed afterdepolarizations coupled to a triggered action potential or from parasystole, can also be considered a manifestation of sustained triggered activity.

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Triggered activity, defined as repetitive activity arising from afterdepolarizations (1), has been implicated in the genesis of certain types of cardiac arrhythmia including paroxysmal tachycardias induced by digitalis (2–8). Triggered rhythms are strongly influenced by the spontaneous or paced rhythm that precedes them, and tend to increase in their rate as the preceding rhythm increases in rate. Their termination may occur suddenly or after a period of gradual slowing.

Recently, we have observed an additional phenomenon during the course of triggered rhythms in ouabain-toxic canine Purkinje fibers: bigeminy resulting from an alternans pattern of the delayed afterdepolarizations that is interposed during otherwise stable triggered activity. In the intact heart, if triggered foci such as these were to assume pacemaker function, the resulting rhythm would appear similar to bigeminy.

Methods

Experimental preparation. Four adult mongrel dogs of either sex were anesthetized with sodium pentobarbital (30 mg/kg body weight intravenously). A right lateral thoracotomy was performed and the heart was rapidly excised and placed into a beaker of cold Tyrode's solution. Free running Purkinje fiber bundles were removed from both ventricles and mounted in a Lucite tissue bath perfused with Tyrode's solution equilibrated with 95% oxygen-5% carbon dioxide. The solution contained (in m*M*): sodium chloride, 131; sodium bicarbonate, 18; calcium chloride, 2.7; magnesium chloride, 0.5; sodium phosphate, dibasic, 1.8; potassium chloride, 4; dextrose, 5.5. Bath temperature was maintained at 37°C and pH was approximately 7.3.

Stimulation protocol. Fibers were stimulated with close bipolar silver wire electrodes coated to the tips with Teflon. Standard techniques were used to stimulate the preparations at a basic cycle length of 500 ms (9). Pulse width was 0.8 ms at 1.5 times the diastolic threshold voltage for stimulation. Standard 3 *M* potassium chloride-filled glass microelectrodes (resistance 5 to 30 MΩ) were used to record transmembrane action potentials from the cells. The electrodes were coupled to a WPI KS-700 amplifier by way of a silver-silver chloride pellet. The tissue bath was connected to ground through a potassium chloride wick coupled to another silver-silver chloride pellet. The action potentials were displayed on an oscilloscope and a strip chart recorder.

After a stable impalement had been maintained for at least 30 minutes, the perfusate was switched to Tyrode's solution containing ouabain, 2×10^{-7} *M*, for 30 to 40 minutes. The drive stimulus was interrupted periodically before ouabain perfusion and every 10 minutes afterward so that any automaticity, delayed afterdepolarizations or triggered activity could be observed. Measurements of cycle length, activation voltage, maximal diastolic potential, action potential duration measured to full repolarization, rate of rise (dV/dt) of the ascending limb of the delayed afterdepolarization and delayed afterdepolarization amplitude and coupling interval to the preceding action potential were made from the strip chart recordings (9,10).

From the Division of Developmental Pharmacology and Departments of Pharmacology and Pediatrics, College of Physicians and Surgeons of Columbia University, New York, New York. This study was supported by Grant HL-28223 from the National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland.

*Present address: School of Veterinary Medicine, University of Pennsylvania, 3800 Spruce Street, Philadelphia, Pennsylvania 19104.

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Address for reprints: Michael R. Rosen, MD, Department of Pharmacology, College of Physicians and Surgeons of Columbia University, 630 West 168th Street, New York, New York 10032.

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Statistics. Data are expressed as mean ± SD and were analyzed using Student's *t* test for nonpaired data (11).

Results

Bigeminy during sustained triggered activity. All of the six Purkinje fiber bundles superfused with ouabain developed delayed afterdepolarizations and sustained triggered activity. In two fibers, this sustained activity had a bigeminal pattern. We studied this further by discontinuing the basic drive stimulus and by interrupting the sustained rhythm intermittently with single electrical stimuli. The action potentials during the bigeminal rhythm had alternating maximal diastolic potential, dV/dt of the delayed afterdepolarization, action potential duration and cycle length.

Figure 1 shows a train of six successive action potentials from one Purkinje fiber that displayed such periodicity. Those action potentials of the form labeled 1 (n = 9) had the following characteristics: activation voltage (AV), −55.0 ± 0.7 mV; maximal diastolic potential (MDP), −80.3 ± 0.4 mV; action potential duration (APD), 263 ± 5 ms; dV/dt of the delayed afterdepolarization, 155 ± 5 mV/s; and cycle length (CL), 412 ± 3 ms. In contrast, the action potentials of the form labeled 2 (n = 8) had the following characteristics: AV, −54.2 ± 1.1 mV; MDP, −78.2 ± 0.3 mV; APD, 250 ± 2 ms; dV/dt, 70 ± 5 mV/s; and CL, 479 ± 6 ms.

All differences between type 1 and type 2 action potentials were significant ($p < 0.05$) except for activation voltage. Action potential amplitude could not be measured accurately from the chart recording because of the inadequate frequency response of the recorder pens. However, the type 1 action potentials consistently had lower amplitudes than those of type 2 (Fig. 1).

Role of alternans pattern in bigeminy. Figure 2 demonstrates that the alternans pattern of the dV/dt of the delayed afterdepolarizations preceded the induction of bigeminy. This trace, obtained shortly after that in Figure 1, shows the effect of interrupting the sustained bigeminal rhythm with single premature depolarizations. Note the small delayed afterdepolarizations and relatively long diastolic intervals immediately after each prematurely induced action potential. The subsequent action potential (A) demonstrates a steep slope of the ascending limb of its delayed afterdepolarization, whereas the next action potential (B) generates a more gradual slope. Despite the immediate occurrence of the alternans pattern after the premature stimulus, the next few impulses show no variation in maximal diastolic potential and no bigeminal pattern in their rhythm. However, with time, the following occurs: the slopes of the delayed afterdepolarizations become more divergent (that is, the slope of action potential A increases and that of action potential B decreases), and this is concomitant with alternation of the maximal diastolic potential of action potentials A and B. With this change in both maximal diastolic potential and in the dV/dt of the afterdepolarizations, the bigeminal pattern emerges.

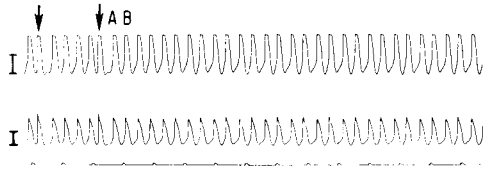


Figure 2. Recording at high (**top**) and low (**bottom**) gains of sustained rhythmic activity for the same Purkinje fiber bundle as in Figure 1. Vertical calibration on the **top** is 15 mV; on the **bottom** it is 25 mV. Maximal diastolic potential is −80 mV. Time marks = 1 second. The sustained rhythm is interrupted by premature stimuli (**arrows**). A and B are the first two action potentials after the premature stimulus. See text for discussion.

Discussion

It is apparent from our experiments that a bigeminal rhythm can occur during sustained triggered activity. This is not the first description of bigeminy occurring in the presence of triggered activity. Previous investigators (2–6,9,12,13) have shown that after driven or automatic action potentials, coupled delayed afterdepolarizations and triggered action potentials may supervene. What makes the

Figure 1. Recording at high (**top**) and low (**bottom**) gains of sustained rhythmic activity from a Purkinje fiber bundle superfused with ouabain. The interval between action potentials (AP) 1 and 2 is 416 ms and is referred to as cycle A; that between action potentials 2 and 1 is 480 ms and is referred to as cycle B. Time marks = 1 second. See text for discussion.

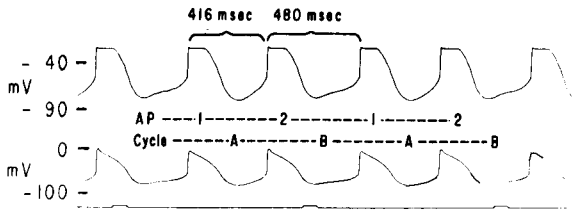
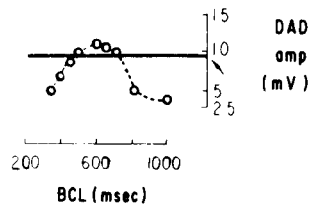


Figure 3. Relation of delayed afterdepolarization amplitude (DAD amp) to basic cycle length (BCL) for a Purkinje fiber. The **arrow** indicates threshold amplitude for inducing triggered action potentials. Previous studies have shown that the rate of rise (dV/dt) of the afterdepolarizations varies with the amplitude (10). See text for discussion.



present pattern different is that during a stable triggered rhythm there is an alternans pattern in maximal diastolic potential and the slope of the delayed afterdepolarization that is responsible for bigeminy.

Is the rhythm triggered, automatic or reentrant? Two questions that arise in considering this phenomenon are 1) Is the rhythm truly triggered as opposed to automatic or reentrant? and 2) What is the explanation for the occurrence of bigeminy and for the alternans pattern in the slope of the afterdepolarization? Considering the first question, several studies have indicated that in the presence of toxic concentrations of digitalis, the normal pacemaker mechanism is suppressed before digitalis-induced triggered activity supervenes (14–16). Nonetheless, abnormal automaticity has been described as a manifestation of digitalis toxicity (10). This rhythm demonstrates an increase in rate after overdrive pacing and, hence, can mimic a triggered rhythm. Because automatic rhythms can generate bigeminal patterns as a result of modulated parasystole (17), the occurrence of automaticity could explain the events we have described. Factors that argue against the involvement of automaticity here are that delayed afterdepolarizations are clearly seen in Figure 2, and that the onset of the rhythm in Figures 1 and 2 was preceded by delayed aftedepolarizations and by the cessation of automatic activity.

As for the possibility of reentry, we were studying unbranched Purkinje fiber bundles that were not of an appropriate geometry for macroreentry. Microreentry might have been the mechanism, but this would be virtually impossible to prove or disprove. The smooth transition between phases 4 and 0 in Figure 1 argues against such a phenomenon.

Figure 3 can be used to explain the events in Figures 1 and 2. In Figure 1, cycle A is 416 ms and cycle B is 480 ms. In Figure 3, the first delayed afterdepolarization would barely be suprathreshold at a cycle length of 416 ms, and it would be of greater amplitude at 480 ms. Hence, cycle A in Figure 1 (416 ms) induces a low, and thus a slowly rising (10), delayed afterdepolarization. This is slow in reaching threshold, giving rise to cycle B of 480 ms. After cycle B, the afterdepolarization has a higher amplitude and more rapid dV/dt, giving rise to the shorter cycle.

What is the explanation for the bigeminy and alternans pattern? It has been shown that delayed afterdepolarizations are voltage-dependent, with individual afterdepolarizations varying in amplitude depending on the membrane potential at which they are initiated (18). In this context, the alternans pattern in maximal diastolic potential can be considered a likely modulator of the amplitude and the slope of the ascending limbs of the afterdepolarizations in Figure 1 and 2, thereby contributing to the bigeminal pattern. However, alternans of the dV/dt preceded that in maximal diastolic potential, making it likely that factors other than membrane potential are the prime determinants. It may be that the present situation represents, for triggered activity, a similar situation to that in modulated parasystole described for automatic rhythms (17) in which electrotonic events influence the lengths of the dysrhythmic cycles.

Clinical implications. The observation of bigeminy appearing during stable triggered rhythms is of interest clinically for the following reasons: in the past, bigeminy was generally assumed to be reentrant, although it was suggested a decade ago (19) that delayed afterdepolarizations induced by a cardiac action potential could trigger coupled action potentials that were clearly bigeminal. Subsequently, some parasystolic rhythms demonstrated bigeminy as well (17). It was assumed that when triggered activity induced bigeminy, the setting would be one of a sinus beat (or an abnormally automatic or reentrant beat) acting as the trigger for the afterdepolarization and extrasystole. It now appears that a rhythm that is, itself, triggered and the result of delayed afterdepolarizations can generate a consistent variation in its afterdepolarization such that a classic bigeminal pattern is seen. Hence, the occurrence of bigeminy interrupting sustained tachycardias may be, in some instances, a variation on the sustained triggered activity. We would expect that in its initiation and termination, its relation to the dominant cycle length of the cardiac rhythm and its response to antiarrhythmic drugs, the behavior of this rhythm would be like that of other forms of delayed afterdepolarization-induced triggered activity (4,5).

Conclusions. We have demonstrated that triggered rhythms induced by delayed afterdepolarizations can show a stable bigeminal pattern as a result of an alternation of the ascending limbs of the afterpolarizations. The significance of this finding is that bigeminal patterns in the presence of delayed afterdepolarizations were previously thought to result only when the first impulse of a couplet was either stimulated or automatic. It now appears that, at least for digitalis-induced triggered rhythms, both action potentials in the bigeminal pair may be triggered, especially in instances where the basic cycle length is between 400 and 600 ms.

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