A Cellular Mechanism for the Generation of Ventricular Arrhythmias by Acetylstrophanthidin

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ABSTRACT

Transmembrane activity was recorded from canine false tendons bathed with Tyrode's solution at 37°C. Stimulus patterns provided a 3-second pause after every ten beats. Acetylstrophanthidin was infused at concentrations up to 2 × 10⁻⁷ g/ml. One or two transient depolarizations (TDs) followed the last driven response of each series. The appearance of TDs was associated with depression of normal phase-4 depolarization. The peak of the earliest TD (TD-1) occurred at an interval approximately equal to the basic cycle length. The later TD (TD-2) occurred at about twice the basic cycle length. Coupling intervals were determined primarily by the last cycle length. The amplitude of TD-1 was maximal when the basic cycle length was 600 msec, but TD-2 continued to increase as the basic cycle length diminished further. The amplitude of both TDs increased with the number of beats in the train. Either or both could reach threshold and induce single extrasystoles or trains of extrasystoles. TDs could be induced to reach threshold after each driven response, resulting in sustained bigeminal rhythms with fixed coupling. Possibly TDs provide a mechanism for various clinically observed arrhythmias induced by cardiac glycosides.

KEY WORDS

transient depolarization  bigeminal rhythm
postpacing depression  cardiac glycosides
Purkinje fibers  repetitive response
ventricular phase-4 depolarization
reentrant rhythm  dog
postpacing acceleration

Cardiac glycosides are believed to cause ventricular arrhythmias by increasing the automaticity of the ventricles. However, automaticity induced by cardiac glycosides or aglycones differs from that associated with normal pacemakers. In the absence of digitalis, the activity of intrinsic pacemakers, whether located in the sinoatrial node or in the His-Purkinje system, is subject to postpacing depression (1). In contrast, Wittenberg et al. (2) have shown that ventricular foci induced by glycosides are accelerated by transient increases in the driving rate. Gandel et al. (3) have reported a similar decrease or reversal of postpacing depression in isolated canine Purkinje tissue treated with ouabain or acetylstrophanthidin. Similarly, the repetitive ventricular response described by Lown et al. (4) might also represent postpacing acceleration of pacemakers: single premature stimuli delivered to the ventricles of a digitalis-intoxicated animal result in one or more "spontaneous" idioventricular responses. Hagemeier and Lown (5) have shown that periods of rapid pacing shorten the coupling interval of the repetitive ventricular response and prolong the period during which the phenomenon can be elicited during recovery from acetylstrophanthidin intoxication.

Ouabain increases the rate of slow diastolic depolarization in isolated Purkinje fibers (6). Also Gandel et al. (3) have reported that rapid driving accelerates slow diastolic depolarization in isolated canine Purkinje fibers exposed to digitalis. This effect might account for the postpacing acceleration observed in situ (2) and for the phenomenon of repetitive ventricular response (5).

In the records published by Lown et al. (4), it appears possible that an accelerated but occult idioventricular pacemaker is exposed during the compensatory pause following an evoked premature ventricular response. If this exposure does indeed occur, then vagally induced interruption of atrioventricular transmission should be followed by a spontaneous idioventricular response at approximately the same escape interval as the repetitive
ventricular response. Experimental test of this hypothesis has shown that the vagal escape interval is often much longer than the induced repetitive ventricular response interval and that the two intervals tend to converge as the atria are driven at progressively higher frequencies (Zipes, Arbel, and Moe, unpublished observations). This result suggests that spontaneous ventricular activity induced by digitalis obeys a different set of rules than does "normal" phase-4 depolarization.

The experiments reported in the present paper were designed to examine the effects of acetylstrophanthidin on isolated Purkinje fibers, to define the conditions under which postpacing depression (as a characteristic of normal pacemaker activity) is replaced by postpacing acceleration of spontaneous activity, and to determine the rules which distinguish drug-induced automatic responses from physiological pacemaker behavior. Acetylstrophanthidin was chosen instead of ouabain because of the greater ease with which a given degree of toxicity could be reached and maintained.

**Methods**

Mongrel dogs (10–25 kg) of either sex were anesthetized with sodium pentobarbital (30 mg/kg, iv). The hearts were excised, and the papillary muscle and its attached false tendon were removed from the right ventricle and transferred to a tissue bath. For some experiments, only the isolated false tendon was used. False tendons excised from the left ventricle also were used. A modified Tyrode's solution equilibrated in a reservoir with 95% O₂-5% CO₂ flowed continuously through the tissue bath at a rate of 10 ml/min. The millimolar composition of the solution was: NaCl 137.0, KC1 4.0, NaH₂PO₄ 0.9, NaHCO₃ 12.0, CaCl₂ 2.5, MgSO₄ 0.5, and dextrose 5.5. The temperature in the tissue bath was maintained at 37°C.

Preparations were driven by rectangular pulses (2–3 msec in duration and twice threshold voltage) obtained from a Tektronix pulse generator (type 161). Stimuli passed through an isolation transformer and were delivered to the false tendon or the apex of the papillary muscle through bipolar silver electrodes. The pulse generator was triggered by a device that permitted the application of a series of regular pulses followed by one or more test stimuli. Each test stimulus could be delivered at any desired interval counted from a 100-kHz crystal oscillator.

Transmembrane action potentials were recorded using glass microelectrodes filled with 2.7M KCl by a method described in detail by Tasaki et al. (7). The resistances of the electrodes ranged from 10 to 25 megohms. Records of transmembrane potentials obtained by conventional techniques were displayed on an oscilloscope (Tektronix 565) and photographed with a Grass camera.

Acetylstrophanthidin¹ was infused into the tissue bath by a Harvard infusion pump. A concentrated solution of the drug (1×10⁻⁴ g/ml) was diluted tenfold with Tyrode's solution and infused at rates to achieve concentrations in the bath from 5×10⁻⁸ g/ml to 2×10⁻⁷ g/ml. The drug entered the bath below the surface of the Tyrode's solution through a hypodermic needle. A small stream of gas (95% O₂-5% CO₂) was continuously bubbled into the bath to disperse the drug.

**Results**

**Transient Depolarizations.**—When isolated preparations of Purkinje tissue, with or without appended ventricular muscle, were driven at a constant frequency during exposure to acetylstrophanthidin in a toxic concentration, apparent acceleration of pacemaker activity occurred. Initially this acceleration was manifest as an increase in the slope of phase-4 depolarization; each evoked action potential occurred during the rising phase of a prepotential. When intoxication was allowed to progress, the frequency of the occult pacemaker exceeded that of the driving stimulator, and a spontaneous tachycardia developed. Ultimately the maximum diastolic membrane potential diminished to the stage of inexcitability. These stages of toxicity can be compared with events recorded in the intact heart: an idioventricular pacemaker, initially occult, can be exposed by vagal stimulation (8) and later becomes manifest as a ventricular tachycardia; eventually, either fibrillation or cardiac arrest occurs.

In the early stage of toxicity, before manifest toxicity developed, we expected stopping the driving stimulator to expose spontaneous pacemaker activity at a frequency somewhat slower than the driven frequency. At this stage, however, interruption of the train of stimuli for a 2- or 3-second period after each tenth stimulus showed that the apparent phase-4 depolarization was in fact the rising phase of the first of one or more subthreshold oscillations (Fig. 1). These oscillations of the membrane potential occurred in all preparations of Purkinje tissue studied (40 preparations) but never in muscle (15 preparations).

Although several low-amplitude, irregular variations in membrane potential sometimes appeared during the pauses in the driving sequence (Fig. 1), only the first one or two, depending on the stimulus pattern, were regularly observed to achieve a

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**Effect of acetylstrophanthidin (1 x 10^-7 g/ml) on the transmembrane potentials of Purkinje fibers (top trace) and muscle (bottom trace) (false tendon-papillary muscle preparation). The first action potential is the last of a train of ten driven potentials (stimulus artifacts are shown below the bottom trace; stimuli delivered to muscle). During the pause in stimulation, two transient depolarizations coupled to the last action potential occur in the Purkinje fiber but not in the muscle. Spikes were retouched.**

The relationships of the amplitudes and coupling intervals of both the TDs to the basic cycle length were studied in ten preparations. The amplitude was measured from the maximum transmembrane potential immediately preceding the TD to the peak of the TD. The coupling interval was measured as the interval from the upstroke of the last action potential to the peak of the TD. The results of a representative experiment are illustrated in Figure 2. The coupling intervals varied directly with the basic cycle length. The coupling interval of TD-1 was approximately equal to the basic cycle length; that of TD-2 was approximately twice the basic cycle length. The amplitude of TD-1 increased as the basic cycle length was decreased from 1000 msec to 600 or 700 msec, but further abbreviation of the basic cycle length resulted in a pronounced decrease in the amplitude. In contrast, the amplitude of TD-2 increased progressively as the basic cycle length decreased. In the illustrated experiment, TD-2 reached threshold when the basic cycle length was decreased below 500 msec. When TD-2 reached threshold, its coupling interval was measured from the upstroke of the last driven action potential to the upstroke of the spontaneous beat. The coupling intervals of the spontaneous beats continued to follow the same relationship with basic cycle length as did subthreshold TD-2s. In some experiments, the coupling interval of TD-2 was considerably greater than twice the basic cycle length at slow driving frequencies, but it was never in excess of three times the basic cycle length.
In addition to the basic driving frequency, the length of the basic train of stimuli also influenced the amplitude of the TDs. Figure 3 illustrates both these factors. In this experiment, the first train consisted of seven stimuli at a basic cycle length of 300 msec. The last action potential of the train was followed by a subthreshold TD-2. TD-1 was absent at this driving frequency. The second train was increased to eight beats at the same cycle length. TD-2 then reached threshold and induced an extrasystole which propagated to the muscle. The final train also contained eight stimuli, but the basic cycle length was increased to 400 msec. At this slower frequency, the last driven beat was followed by a low-amplitude TD-1 and a larger TD-2, neither of which reached threshold. The increase in cycle length resulted in an increase in the amplitude of TD-1 (from zero) and a decrease in the amplitude and the slope of TD-2.

The results illustrated in Figure 3 suggest a cumulative effect of driving frequency on the amplitudes and the coupling intervals of the TDs, but they do not indicate the relative importance of the last cycle length in the train. The effect of varying the last cycle length while keeping the preceding cycle lengths constant was examined in 11 experiments. The results of one of these experiments, in which the basic cycle length was 500 msec, are illustrated in Figure 4. The general relationships were similar to those observed when the basic cycle length was altered (Fig. 2); however, the slopes of the lines describing the changes in coupling intervals were less steep. When the last cycle length was double the basic cycle length, i.e., 1000 msec, the coupling interval of TD-1 was about 700 msec; as the test interval approached the basic cycle length, the coupling interval of TD-1 approached 500 msec, as predicted by Figure 2. The diminished amplitude of TD-1 at briefer test intervals precluded measurement of coupling intervals. The coupling interval of TD-2 as a function of the last cycle length also showed a cumulative effect. With the longest test cycle, the coupling interval was less than twice the preceding cycle length; with the

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**FIGURE 3**

Effect of train length and basic cycle length (BCL) on the amplitude of TD (false tendon-papillary muscle preparation, stimuli delivered to the apex of the papillary muscle). The top trace is from a Purkinje fiber in the false tendon, the middle trace is from the muscle, and the bottom trace shows the stimulus pattern. TD-2 was subthreshold following seven driven responses at a basic cycle length of 300 msec. Increasing the train to eight driven action potentials resulted in TD-2 reaching threshold, and an extrasystole was propagated to the muscle. When the basic cycle length was increased to 400 msec, the TD was again subthreshold. TD-1 only appeared when the basic cycle length was 400 msec. Spikes were retouched.

**FIGURE 4**

Relationships between the coupling intervals and amplitudes of both TDs and the cycle length preceding the last driven response. Trains of ten stimuli were followed by 3-second pauses. Basic cycle length (BCL) was constant at 500 msec, but the last cycle length varied from 200 to 1000 msec. Format and measurements are the same as in Figure 2.
shortest test cycle, it was about three times the preceding cycle length. The decreases in slope indicate that there is a cumulative effect of preceding cycle lengths on the coupling intervals of the TDs. The relationships between the amplitudes of the TDs and the last cycle length were similar to those with the basic cycle length.

The number of driven beats in each train greatly affected the amplitudes of the TDs. This relationship was studied in 24 preparations. Figure 5 illustrates a representative experiment. The figure shows the relationship for TD-1 at the basic cycle length at which its amplitude was maximal; that for TD-2 was recorded at a briefer basic cycle length, at which the amplitude of the TD was relatively high but still subthreshold. The amplitudes of both TDs increased with the number of beats in the train, reaching a relatively constant value after seven to ten beats. The number of beats in each train had almost no effect on the coupling intervals of the TDs. The only consistent effect observed was that the coupling interval of TD-2 was long following the first interval.

The trains of driven beats were frequently followed by more than one spontaneous response. Multiple responses were more common in preparations which allowed to become progressively more toxic after the first single spontaneous beats were observed. An example of multiple responses is shown in Figure 6. The stimulus trains contained six stimuli. In Figure 6A, the basic cycle length was 800 msec, and the driven train was followed by a subthreshold TD-1; TD-2 was not apparent at this slow frequency. Figure 6B shows the effect of decreasing the basic cycle length to 700 msec. TD-1 reached threshold and caused a spontaneous beat that was in turn followed by another TD-1. When the basic cycle length was shortened to 600 msec (C), the coupling interval of the spontaneous beat was decreased, and the following TD-1 also reached threshold and caused a second spontaneous action potential followed by a subthreshold TD-1. A further decrease in the basic cycle length to 500 msec (D) caused the TD-1 following the first two spontaneous beats to reach threshold and generate yet another spontaneous action potential. The three spontaneous beats were followed by a subthreshold TD-1.

Preparations allowed to become even more toxic showed long trains of spontaneous beats followed by subthreshold TDs. An example of one such sequence is shown in Figure 7. In this instance the preparation had not been stimulated, nor was it spontaneously active, during the preceding 20 seconds. We observed that following long quiescent periods cumulative effects of pacing lasted for several trains of beats. This phenomenon also is illustrated in Figure 7. The first train of driven responses (basic cycle length 400 msec) resulted in one spontaneous beat followed by a subthreshold TD. Following the second train of stimuli, three

![Figure 5](image)

**Figure 5**

Relationships between the coupling intervals and amplitudes of both TDs and the number of driven responses in each train. Left: Relationships for TD-1; basic cycle length (BCL) was 600 msec. Right: Relationships for TD-2; basic cycle length was 400 msec. Measurements are the same as in Figure 2.

![Figure 6](image)

**Figure 6**

Multiple responses due to transient depolarizations. Top traces were recorded from the isolated false tendon, and bottom traces show the stimulus pattern. Spikes were retouched. BCL = basic cycle length.
TDs reached threshold. Finally, the third train induced 15 spontaneous discharges at a gradually decelerating rate followed by one subthreshold TD. The coupling interval of the TD was equal to the last spontaneous cycle length, and this TD was therefore designated a TD-1. No phase-4 depolarization was observed for 14 seconds following the last action potential initiated by a TD. At this level of toxicity, trains of beats generated by TDs often lasted several minutes and on several occasions continued until the preparation depolarized and became inexcitable.

**Phase-4 Depolarization.**—We found in nearly all preparations that acetylstrophanthidin greatly suppressed slow diastolic depolarization. Before treatment, escape intervals ranged from 20 to 60 seconds. In five experiments in which stimulation was stopped when a TD reached threshold, no phase-4 depolarization occurred during 10 minutes of observation. More commonly, escape intervals ranged from 90 to 180 seconds. In two preparations, the escape intervals following exposure to acetylstrophanthidin were brief enough to permit study of the relationship between the escape interval and the preceding duration of pacing. The results of one of these studies are illustrated in Figure 8. Before infusion of acetylstrophanthidin, the escape interval increased as the duration of pacing increased.

Following infusion of acetylstrophanthidin, the escape intervals were increased for all durations of pacing. Also the initial portion of the curve was much steeper. After the acetylstrophanthidin was allowed to wash from the bath, the relationship returned approximately to control. The results indicate that postpacing depression of phase-4 depolarization was enhanced by acetylstrophanthidin at a time when TDs were readily demonstrable.

In the experiment illustrated, pacemaker activity was allowed to reach a constant interval between pacing trials. During the pretreatment control period, the interval was $3.9 \pm 0.8$ seconds. Acetylstrophanthidin caused the interval to increase to $14.6 \pm 2.3$ seconds. After the drug was removed from the bath, the interval of discharge shortened to $5.0 \pm 0.8$ seconds. The results suggest that acetylstrophanthidin might slow pacemaker activity as well as enhance postpacing depression.
Reentry.—In several experiments on false tendon-papillary muscle preparations, repetitive activity that could not be attributed to TDs was observed. Although some driving frequencies were more effective than others in precipitating this activity, the spontaneous discharges did not exhibit the relationships to basic cycle length and train length described for TDs. The spontaneous action potentials occurred immediately following repolarization of the driven responses and appeared with equal frequency following one or two driven responses or following long driven trains. Also the phenomenon was not particularly stable: a procedure that elicited spontaneous discharges one time could fail to do so in a second trial a few seconds later. Activity of this type might have been caused by reentry involving the attached muscle, since it was never observed in false tendons isolated from muscle.

The question might arise as to whether TDs are electrotonic images of reentrant activity at some distance from the recording site. If this supposition were so, TDs should be closely coupled to the preceding action potential, and it should be possible to locate the reentrant action potentials responsible for the electrotonic images. In all experiments, recordings were made at several sites. TDs were always synchronous at all sites, although in some experiments the impalements were separated by several space constants (up to 12 mm).

In one experiment, an isolated false tendon (3.6 mm in length) was examined using a reference impalement at one site and an exploring electrode that was moved through a sequence of 22 recording sites. A basic cycle length of 450 msec was used so that both TDs would be present. The TDs were synchronous at all sites. No evidence of a reentrant action potential was found. In all experiments when TDs first reached threshold, the action potential could be recorded at all sites.

Bigeminal Rhythms.—Complex arrhythmias were often observed. Bigeminal rhythms were generated in ten preparations. Figure 9 illustrates an example of bigeminal rhythms induced in an isolated false tendon by bursts of rapid stimulation (basic cycle length 300 msec) interpolated during continuous stimulation at a slower rate (basic cycle length 900 msec). Figure 9A shows the effect of interpolating a short train of rapid beats without a resultant bigeminal rhythm. The last of the rapid beats was followed by a TD-2 that reached threshold. The coupling interval of the spontaneous beat was 660 msec. The first stimulus delivered at the 900-msec cycle length fell during the refractory period of the spontaneous beat. The remaining eight stimuli delivered at the long cycle length resulted in action potentials. Stimulation was then stopped to demonstrate a subthreshold TD generated by the 900-msec interval and to show the absence of spontaneous pacemaker activity. No activity was observed in a total pause of 6 seconds. Figure 9B illustrates a sequence resulting in a short train of coupled beats. The train of rapid beats resulted in a TD which reached threshold at a coupling interval of 600 msec; the first stimulus delivered at 900 msec fell after the refractory period and resulted in an active response, which in turn followed by a spontaneous discharge arising from the peak of a TD. The cycle of long and short intervals repeated several times. The coupling intervals of the spontaneous beats alternated during this sequence (intervals: 600, 580, 640, 580, and 670 msec). The longer interval of the last coupled beat left the tissue refractory at the time when the next stimulus arrived and terminated the episode of...
bigeminal rhythm. The TDs resulting in coupled beats were probably TD-2s, because the coupling intervals were approximately equal to twice the preceding intervals. The terminal TD occurred at an interval approximately equal to the preceding interval and therefore was probably a TD-1. Figure 8C illustrates a sequence similar to the preceding one except that the coupling intervals of the spontaneous beats were more uniform and the bigeminal rhythm was terminated only by the occurrence of the next train of rapid beats. Figure 9D demonstrates that, in the absence of the stimuli delivered at 900-msec intervals, multiple responses did not occur.

In some experiments, a bigeminal pattern developed during continuous driving at a slow frequency, without the interpolation of a period of rapid pacing. In these instances the coupling interval of TD-1 was slightly less than the basic cycle length. The amplitude increased gradually until threshold was reached. The resulting alteration of cycle length permitted the development of a response pattern similar to that in Figure 9.

Termination of Self-Sustained Rhythms.—In two experiments with isolated false tendons, we abruptly terminated tachycardias caused by TDs by interpolating premature responses. Figure 10 illustrates one of these experiments. In A, three driven responses at a cycle length of 300 msec were followed by a train of 14 spontaneous beats. The coupling interval of the first spontaneous beat was 590 msec, suggesting that a TD-2 initiated this beat. The cycle length of the following beats progressively decreased from 470 msec to 420 msec, indicating that TD-1s initiated each of these action potentials.

A premature stimulus delivered 230 msec after the fourteenth spontaneous beat was followed by a suprathreshold TD-2 at a coupling interval of 470 msec. This final action potential was followed by a large subthreshold TD-1 at 430 msec and a smaller TD-2 at 900 msec. A similar sequence was repeated 2.8 seconds after the subthreshold TD-2 (B). The second tachycardia was terminated by a premature response after 11 spontaneous beats; the terminal events were similar to those in A.

It is not clear how the premature response terminated the tachycardia. The slope of the upstroke of the final subthreshold TD-1 was at least as great as that preceding each beat of the spontaneous train. However, the maximum diastolic potential achieved before the subthreshold TD was less than that observed during the train. The mechanism of termination might be explained if the observed incomplete repolarization was accompanied by incomplete recovery of excitability.

Discussion

The TDs described in this study were early manifestations of digitalis intoxication. They appeared at a time when the maximum diastolic membrane potential of the impaled Purkinje fibers was still in excess of 75 mv, and they were responsible for the earliest ectopic activity observed. They appeared to be distinctly different from normal phase-4 depolarization. Pacemaker activity exhibits postpacing depression, whereas the coupling interval of TDs was abbreviated as the pacing frequency was increased. TDs also appeared to be distinctly different from the oscillations associated with phase-4 depolarization as described by Vassalle (9). Oscillatory potentials of this type gradually increase in amplitude and finally initiate pacemaker activity. Also, pacemaker activity, when depressed by high potassium, can terminate with progressively diminishing oscillations. In contrast, TDs were never observed to behave as a series (greater than two) of progressively increasing oscillations leading to repetitive suprathreshold activity.

The characteristic relationships between the preceding cycle length and the amplitudes and coupling intervals of both TD-1 and TD-2 were foreign to normal phase-4 depolarization or associated oscillations. In fact, the observation that acetylstrophanthidin caused TDs but depressed pacemaker activity is, in itself, a differentiating factor. Finally, enhancement of postpacing depression by acetylstrophanthidin was demonstrated at a
time when the frequency-dependent TDs were also present. This observation strongly suggests that TDs differ from normal phase-4 depolarization and might indicate a possible difference in mechanism.

Previous work has suggested that cardiac glycosides increase the automaticity of the ventricles by enhancing phase-4 depolarization (3, 6). However, Vassalle et al. (10) and Wittenberg et al. (11) have reported that frequently the idioventricular rate of dogs progressively intoxicated with ouabain first decreases and only later increases. In some cases the depression of ventricular automaticity is so marked that vagal stimulation results in cardiac standstill (10). This diphasic action of ouabain on ventricular automaticity might be explained by the present study. During the early stage of intoxication when TDs were regularly seen, we never observed enhancement of phase-4 depolarization by acetylstrophanthinid. In fact, acetylstrophanthinid suppressed phase-4 depolarization and enhanced postpacing depression of any residual activity. The initial depression of automaticity observed by Vassalle et al. (10) and Wittenberg et al. (11) might be due to this action. Subsequent enhancement of ventricular automaticity might be caused by transient depolarizations rather than by a reversal of the inhibition of phase-4 depolarization.

It is possible that in earlier in vitro studies the upstroke of TD-1 was mistaken for normal pacemaker activity. The characteristics of TDs are such that they explain observations previously attributed to phase-4 depolarization. The coupling intervals of spontaneous beats generated by TDs varied directly with the preceding cycle lengths. This effect, plus cumulative effects, could mimic the postspacing acceleration observed by Wittenberg et al. (10) and Gandel et al. (3) and attributed to an alteration in the characteristics of phase-4 depolarization. Similarly repetitive ventricular responses described by Lown et al. (4) are more easily elicited when the initiating extrasystoles are preceded by rapid stimulation (5). Preceding short cycles also shorten the coupling interval of the repetitive ventricular response. The effect of rapid stimulation, which increased the amplitude and decreased the coupling interval of TD-2, might explain these observations. The ability of a single premature beat to elicit a repetitive ventricular response when none occurs with a simple pause also is consistent with the effect of the last cycle length on the amplitude and the coupling interval of the TDs.

Bigeminal rhythms are often attributed to reentry because of the constant coupling intervals and the dependency on initiating beats (10). However, the present study demonstrated that TDs, which are not a manifestation of reentry, can provide both constant coupling intervals and a dependency on initiating beats. Vassalle et al. (10) have also shown in intact dogs that increased sinus node activity often results in trains of idioventricular beats. Atioventricular block induced by vagal stimulation does not affect previously initiated tachycardias but prevents the start of new tachycardias. During vagal stimulation, ventricular arrest follows if the tachycardias spontaneously end. Tachycardias of this type have been discussed as possible reentrant arrhythmias. Also, termination of a tachycardia by a single premature beat has been considered to be indicative of a reentrant mechanism (12). The premature beat is thought to interrupt a reentrant loop by rendering part of the pathway refractory at a time that extinguishes the circus movement. Tachycardias initiated by TDs shared these characteristics. It is clear that the present criteria for identifying reentry cannot distinguish arrhythmias caused by digitalis-induced TDs from arrhythmias truly caused by reentry.

TDs, if they occur in the intact heart, might be responsible for many arrhythmias resulting from glycoside intoxication; the present study provides a partial explanation for the peculiarities encountered in the treatment of arrhythmias induced by glycosides. Further studies might explain the special antiarrhythmic efficacy of diphenylhydantoin and the lack of success of cardioversion observed in the clinical treatment of arrhythmias caused by cardiac glycoside intoxication.

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