Characteristics of initiation and termination of catecholamine-induced triggered activity in atrial fibers of the coronary sinus

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ABSTRACT We studied epinephrine-induced delayed afterdepolarizations and triggered activity in atrial fibers from the canine coronary sinus to determine whether their responses to cardiac pacing would aid in formulating a uniform set of guidelines for differentiating this triggered activity from other arrhythmogenic mechanisms. We used standard microelectrode techniques and compared the delayed afterdepolarizations and triggered activity with those occurring in ouabain-superfused Purkinje fibers. Like Purkinje fibers, the frequency of triggering in the coronary sinus and the coupling interval of the first triggered beat were related directly to the basic drive cycle length, and the delayed afterdepolarization amplitude and frequency of triggering were related to the coupling interval of premature stimuli (S₂). However, unlike Purkinje fibers, the coupling interval of the delayed afterdepolarization and of the first triggered beat were independent of the S₂. Once initiated, triggered activity in the coronary sinus followed one of four rhythm patterns: in all four, the minimum and equilibrium cycle lengths were independent of the initiating cycle length. Triggered activity was terminated by overdrive and S₂ pacing, especially by long episodes of overdrive at short cycle length. The first escape beat after overdrive was linearly related to the overdrive cycle length, resulting in overdrive acceleration. The return cycle length after S₂ was linearly related to the S₂ coupling interval. Because delayed afterdepolarizations and triggered activity in the coronary sinus respond differently to pacing from those in ouabain-superfused Purkinje fibers, triggered activity in general may not be identified by a uniform set of guidelines.


TRIGGERED ACTIVITY resulting from delayed afterdepolarizations has been studied in digitalis-toxic Purkinje fibers,¹⁻³ catecholamine-treated atrial fibers of the coronary sinus,⁶,⁷ experimental myocardial infarction,⁸,⁹ various other atrial¹⁰⁻¹² and ventricular¹³⁻¹⁷ tissues under a variety of experimental conditions, and in human atrial¹⁸⁻²⁰ and ventricular²¹ fibers in vitro. It has been proposed that triggered activity is a cause of arrhythmias, but it is difficult to distinguish this mechanism from other arrhythmogenic mechanisms. One approach to the problem of identifying triggered rhythms has been to define a characteristic pattern of responses to pacing, which can be documented in the microelectrode laboratory and then applied to the setting in vivo.¹²,¹³ For example, the characteristics of triggered activity described in digitalis-toxic Purkinje fibers have been applied successfully to the identification of digitalis induced arrhythmias in the intact animal²⁴,²⁵ and, by implication, in patients.²²,²³ It has been tempting to apply these observations of digitalis-induced triggered activity more generally to predict the behavior of other types of triggered activity that might occur clinically. However, observations made to date in atrial fibers of the coronary sinus⁶,⁷ suggest that such extrapolation might be inappropriate. If this is the case, then triggered arrhythmias induced by mechanisms other than digitalis toxicity might, mistakenly, not be identified as triggered simply because they failed to conform to the "rules" suggested for digitalis.⁵,²²,²³

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For this reason we quantified the characteristics of initiation and termination of triggered activity in the atrial fibers of the canine coronary sinus and the afterdepolarizations that induce it. In so doing, we were aware of the limitations inherent in attempting to extrapolate from any given model to the intact heart but were nevertheless encouraged by the results of a similar approach used to quantify rhythms induced by digitalis toxicity. We have found that there are some similarities between the triggered rhythms induced by catecholamines in atrial fibers of the coronary sinus and those caused by digitalis in Purkinje fibers, but there are important differences as well. These must be considered carefully in attempting to define the behavior of triggered activity in experimental animals and in the clinic.

Methods

Adult mongrel dogs weighing 10 to 25 kg were anesthetized with sodium pentobarbital (30 mg/kg iv). Their hearts were removed quickly through a right thoracotomy and immersed in cold Tyrode's solution of the following millimolar composition: NaCl 131, NaHCO3 18, KCl 4, NaH2PO4 1.8, MgCl2 0.5, CaCl2 2.7, and dextrose 5.5. The solution had been equilibrated with 95% O2 and 5% CO2. The coronary sinus was removed en bloc and opened via a longitudinal incision of the roof, as previously described. The sinus was then pinned out flat with the luminal surface down. Under a dissecting microscope, excess connective tissue and fat were trimmed away, leaving a muscle layer less than 0.5 mm thick attached to the endothelial membrane. Small strips (1 x 3 mm) were cut from the distal half of this tissue and secured by two stainless-steel insect pins in a Sylgard-lined tissue bath. The tissue bath was perfused with Tyrode's solution maintained at 37.0 ± 0.25°C by a glass heat exchanger. The flow rate was 13 ml/min, so that the bath volume was changed every 45 sec.

Preparations were stimulated via bipolar Teflon-coated silver wires with square pulses of 0.75 to 1.5 msec duration and amplitudes 1.5 to 2 times threshold. Premature stimuli (S1) had amplitudes and durations 1.5 to 2 times those of the basic drive stimuli (S2). When S2 stimuli followed S1, the S2 were triggered and delayed from the preceding S1. During episodes of triggered activity, the differentiated upstrokes of the spontaneous action potentials were used to trigger the S2.

We recorded transmembrane potentials via 3M KCl-filled glass capillary microelectrodes with tip resistances of 20 to 40 MΩ. The signals were channeled through an amplifier with high input impedance and capacity neutralization and were displayed on an oscilloscope and a strip-chart recorder. We measured delayed afterdepolarization amplitude from the preceding maximum diastolic potential to the peak of the afterdepolarization, and coupling interval from the upstroke of the preceding action potential to the peak of the afterdepolarization. In addition, we used a tachometer, triggered by the differentiated phase 0 upstroke of the action potential, to record the beat-to-beat cycle length of triggered rhythmic activity on the strip-chart recorder. We used previously described techniques to calibrate the equipment.

Effects of pacing on delayed afterdepolarizations and on induction of triggered activity. We found (as previously described by Wit et al.5,23) that failure to stimulate a coronary sinus preparation results in its depolarization. This was the situation for many of the preparations we studied, when they were initially placed in the tissue bath. We therefore drove the preparations for the first hour at a cycle length of 400 msec and induced hyperpolarization to a normal membrane potential (presumably via Na-K pumping). We then continued to drive at a more physiologic cycle length of 1000 msec, allowing several minutes of equilibration after the change in cycle length. The superfusate then was changed to one containing EDTA (5 x 10⁻⁴ M) and l-epinephrine d-bitartrate (5 x 10⁻⁵ M) to induce delayed afterdepolarizations. The epinephrine concentration was increased at 10 min intervals until a delayed afterdepolarization of approximately 10 mV amplitude was produced at the drive cycle length of 1000 msec. The final concentration of epinephrine required to attain this result varied from 5 x 10⁻⁵ M to 2 x 10⁻⁶ M. Action potential measurements were made again in the presence of the final epinephrine concentration.

The effect of epinephrine on delayed afterdepolarization amplitude required about 10 min to reach equilibrium at any given concentration. For this reason, all changes of superfusate epinephrine concentration were followed by at least a 10 min equilibration period before measurements were made. In addition, during maintenance of a constant concentration of epinephrine over longer periods (1 to 3 hr), the delayed afterdepolarization amplitude eventually began to decline, presumably because of desensitization. To minimize the influence of this gradual decay on our results, pacing protocols were performed in varied sequences.

To determine the relationship between drive cycle length and the delayed afterdepolarizations, we first evaluated the afterdepolarizations produced by 15 driven beats at each of 13 basic drive cycle lengths from 200 to 1500 msec in varied sequences. The amplitude of developed delayed afterdepolarizations rapidly increased over the first 8 to 12 beats of a driven series. For this reason, all test runs consisted of 15 driven beats to ensure that an equilibrium afterdepolarization amplitude had been attained. To minimize the possible effect of membrane potential on afterdepolarizations, each test run within a given group was initiated at approximately the same level of membrane potential (range, ± 2 mV in each experiment).

To study the delayed afterdepolarizations produced by premature stimuli, 15 driven beats at basic drive cycle lengths of 1000, 800, and 600 msec were followed by an S2. We tested S2 coupling intervals equal to all multiples of 100 msec from 1000 through 300 msec. In addition, S2 coupling intervals of 300 msec or less we tested all multiples of 20, 10, 5, and 2.5 msec. All 15 beat trains were initiated at approximately the same membrane potential, and all S2 coupling intervals were tested in varied sequences. To evaluate the frequency of triggering, we made two to three repetitions of the stimulation protocol and calculated the percentage of trials that resulted in triggered activity for each preparation at each basic cycle length or S2 coupling interval. These percentages then were averaged across all of the preparations to give a mean triggering frequency corresponding to each basic cycle length and each S2 coupling interval.

When triggered activity occurred, the coupling interval of the first triggered beat was measured from the upstroke of the last driven action potential to the upstroke of the first triggered action potential.

Effects of pacing on triggered activity. To evaluate the effect of pacing interventions on triggered activity, the epinephrine concentration of the superfusate was further increased until prolonged periods of triggered activity (over 25 beats) were readily initiated by a short drive train at a cycle length of 1000 msec. The epinephrine concentration required to accomplish this ranged from 5 x 10⁻⁵ M to 1 x 10⁻⁴ M. Only those preparations in which the first episode of triggered activity
persisted for at least 5 min were chosen for the evaluation of pacing interventions. Subsequent triggered rhythms were subjected to pacing interventions once they had persisted for at least 2 min. Overdrive pacing was tested at 50% and 75% of the preceding triggered cycle length for sequences of 15, 30, 60, and 120 paced beats. These interventions were tested in varied sequences. An interval of at least 30 sec was allowed between overdrive interventions. Similarly, in other trials, single S2 were introduced after every thirtieth triggered beat. The S2 coupling interval scanned the diastolic period in multiples of 10 msec in varied sequences. Both pacing protocols were repeated at least three times. Termination was defined for both types of intervention as cessation of the triggered rhythm within 50 beats of the last paced impulse. Abrupt termination, in which a delayed afterdepolarization but no action potentials followed the last paced beat, was distinguished from delayed termination, in which 1 to 30 triggered beats followed the last paced beat. The frequency of termination was determined for each preparation, and means were then calculated from all preparations for each type of intervention.

In instances when a pacing intervention was followed by at least one triggered beat, the escape cycle length (in the case of overdrive) and the return cycle length (in the case of S2) was measured from the upstroke of the last driven action potential to the upstroke of the first triggered action potential. Since the rate of the triggered rhythm was variable over time and between preparations, the corrected pacing cycle lengths and escape intervals were calculated by dividing each value by the preceding triggered cycle length.

Data analysis. Only those experiments in which the same impalement was maintained throughout the entire range of test cycle lengths or coupling intervals were used to evaluate delayed afterdepolarizations. We used a paired t test to compare control action potential variables with those recorded after epinephrine superfusion. Point-by-point comparison by the Scheffé test was applied to the amplitudes and coupling intervals of delayed afterdepolarizations after drive plus S2 when permitted by analysis of variance (ANOVA).

The mean frequencies of triggering were modified by the arcsine transformation before statistical analysis to bring the variance of data near the extremes of 0% and 100% closer to the variance of data near 50% on the proportional scale. These data then were evaluated by ANOVA. Mean frequencies of termination after overdrive pacing were transformed by the arcsine conversion for the same reasons. With these transformed data, comparisons between frequency of termination after short and long durations of overdrive, and between short and long overdrive cycle lengths were made with the paired t test.

Escape cycle lengths after overdrive and return cycle lengths following S2 were divided by the triggered cycle length preceding each intervention to yield “corrected” values. Return cycle lengths following S2 were analyzed by linear regression, and the significance of the correlation coefficient was determined for each preparation. All other data were analyzed by ANOVA or nested ANOVA. Data are presented as mean ± SEM.

Results

Effect of epinephrine. Eighty-three preparations (from 40 dogs) were initially equilibrated in Tyrode’s solution at a drive cycle length of 400 msec. When the cycle length was increased to 600 msec, 4% of the preparations gradually depolarized and became inexcitable. Twenty-six percent of the preparations depolarized and were inexcitable at a drive cycle length of 1000 msec. Some of these hyperpolarized and recovered excitability during the subsequent superfusion with epinephrine and were included in the study of delayed afterdepolarizations and triggered activity.6, 28, 29, 32

Action potential variables were measured in the control state for those preparations that had stable transmembrane potentials at a drive cycle length of 1000 msec, and again after addition of the concentration of epinephrine needed to produce a delayed afterdepolarization of 10 mV amplitude (6 × 10⁻⁴M to 2 × 10⁻⁶M). In 19 preparations the same impalement was maintained throughout the process of epinephrine superfusion. The control transmembrane potential characteristics and effects of epinephrine were, respectively, maximum diastolic potential, −82 ± 1.3 and −88 ± 1.4 mV (p < .01); amplitude, 109 ± 2 and 120 ± 2 mV (p < .01); Vmax, 179 ± 12 and 215 ± 14 V/sec (p < .01); action potential duration to 50% and 90% repolarization, 84 ± 5 and 88 ± 4 msec, and 201 ± 6 and 177 ± 5 msec (p < .01), respectively. Neither delayed afterdepolarizations nor triggered activity were seen during the control period, but delayed afterdepolarizations always appeared during epinephrine superfusion, their amplitude increasing with the concentration. Triggered activity was more readily induced and the cycle length of triggered rhythms decreased as the concentration of epinephrine was increased.

Effect of membrane potential on delayed afterdepolarizations. The amplitude of delayed afterdepolarizations occurring in digitalis-superfused Purkinje fibers is influenced by the membrane potential.28, 29 Similarly, in atrial fibers of the coronary sinus the transient inward current underlying the afterdepolarizations is dependent on membrane potential.30 The lability of the membrane potential of atrial cells in the coronary sinus is demonstrated in the top panel of figure 1. Even in the presence of epinephrine, periods of either driven or triggered activity were accompanied by hyperpolarization of the membrane potential and periods of quiescence were accompanied by depolarization.7

Figure 1 also shows the extent to which membrane potential variations resulting from performance of the pacing protocol may influence the measurement of delayed afterdepolarizations. As the membrane potential decreased, the amplitude of the delayed afterdepolarizations increased several fold and their coupling interval to the preceding action potential decreased. Whereas the curves in figure 1 relate delayed afterdepolarizations to the membrane potentials at which they were induced (activation voltage), it should be empha-
the drive cycle length was 400 msec or less. When these second afterdepolarizations were seen, they were always less than 50% of the amplitude of the first and occurred at a coupling interval that was two to three times the coupling interval of the first. Over the course of the entire study, triggered activity was never initiated by a second afterdepolarization.

The amplitude of the delayed afterdepolarizations increased exponentially as the basic drive cycle length decreased, as shown in figure 2 and summarized in the top panel of figure 3. This behavior is comparable to that of the second delayed afterdepolarization occurring in digitalis-superfused Purkinje fibers. The coupling interval, summarized in the bottom panel of figure 3, decreased with the basic drive cycle length in a linear fashion between cycle lengths of 1500 and 500 msec.

Twenty-one of 22 preparations developed delayed afterdepolarizations of sufficient amplitude to induce triggered activity (as in figure 2). The relationship of the frequency of triggering to basic cycle length (figure 4, top) was similar in contour to the curve relating delayed afterdepolarization amplitude to basic cycle length (figure 3, top). The relationship of the coupling interval of the first triggered beat to basic cycle length is shown in the bottom panel of figure 4. These curves indicate that triggered rhythms are more readily induced by drive trains of short cycle length, and once induced, the coupling interval of the first triggered beat varies directly with the initiating drive cycle length.

**Influence of S2 on delayed afterdepolarizations.** We delivered 15 stimuli at basic cycle lengths of 1000, 800, or 600 msec, followed by an S2 at numerous coupling intervals selected in varied sequence. Figure 5 shows the results of this protocol. As the basic cycle length decreased from 1000 to 600 msec, the curves relating delayed afterdepolarization amplitude to the S1-S2 interval were displaced to higher values and the coupling interval curves were displaced to lower values, as expected from the relationship shown in figure 3 for basic drive alone. In addition to this effect, delayed afterdepolarization amplitude continued to increase in response to S2 of increasing prematurity. This effect of the S2 became significant only when the S2 occurred very early. At basic cycle lengths of 1000 and 800 msec, the delayed afterdepolarization coupling interval decreased significantly with the first S2, but no further shortening of the coupling interval was seen at shorter S1-S2 intervals. At the shortest basic cycle length, 600 msec, the S2 had no additional effect on the delayed afterdepolarization coupling interval.

At a basic cycle length of 1000 msec, five of 14
FIGURE 2. Effect of basic drive cycle length (BCL) on delayed afterdepolarizations. Trains of 15 beats of decreasing cycle lengths produced afterdepolarizations of increasing amplitude and decreasing coupling interval. The afterdepolarization following the last train (BCL = 200 msec) reached threshold and triggered four action potentials.

FIGURE 3. Effect of basic drive cycle length on delayed afterdepolarization amplitude (top) and coupling interval (bottom) (n = 9).

preparations (36%) developed delayed afterdepolarizations of sufficient amplitude to induce triggered activity in response to the basic drive plus an S2. This is a markedly greater frequency of triggering than that produced by basic drive alone at the same cycle length (see figure 4). In addition, when the frequency of triggering was expressed as a function of the S1-S2 coupling interval (figure 6, top), the triggering frequency increased as the S2 became more premature. In contrast, the coupling interval of the first triggered beat was not influenced by the degree of prematurity of the S2 (figure 6, bottom).

Characteristics of prolonged triggered rhythms. A mean of 18 episodes of prolonged triggered activity were observed in each of 38 preparations. They followed one of the four characteristic patterns that are presented in figure 7. Seventy-nine percent of all episodes had a characteristic warm-up phase to a minimum cycle length like the examples in panels B and C. In 22 preparations (14% of all episodes), particularly in the case of shorter bursts of triggered activity, or after the use of a rapid initiating drive rate, the triggered rhythm would slow from the first or second triggered beat, as in panel A. The pattern of onset shown in panel D,
where the rhythm initially slowed and then accelerated, was seen in only 10 preparations (7% of all episodes). Some triggered rhythms (34% of all episodes) achieved a steady-state cycle length (as in panel C) and these tended to be longer in duration than those that attained no steady state (panels A, B, and D). These four characteristic patterns of triggered activity were not specific to a given preparation; rather, two or three different patterns usually occurred in the same preparation. As previously described, all triggered rhythms demonstrated a slowing trend just before termination, some more prominently than others.  

We further evaluated the cycle length of triggered activity as follows: we measured the minimum cycle length attained in episodes of triggered activity initiated over a range of drive cycle lengths from 200 to 1000 msec in 15 preparations. The mean minimum cycle length (404 ± 11 msec) was constant, independent of the drive cycle length at which the triggered activity had been initiated. In addition, in those preparations that developed a stable rhythm (e.g., figure 7, C), the mean equilibrium cycle length (524 ± 49 msec) was constant over the same wide range of initiating drive cycle lengths. This means that although the coupling interval of the first triggered beat was dependent on the cycle length of the initiating drive (as demonstrated in figure 4), the minimum and equilibrium cycle lengths of the resulting triggered rhythm were not.

We then considered the influence of membrane potential on the characteristics of the triggered rhythms. This was similar to that described for delayed afterdepolarizations in figure 1. A transmembrane potential recording of two sequential episodes of prolonged triggered activity is shown in the top panel of figure 8. The membrane hyperpolarized with activity and then depolarized during the intervening period of quiescence. By initiating the second episode of triggered activity after different intervals of quiescence, we varied the activation voltage of that episode. As shown in the bottom panel of figure 8, the minimum triggered cycle length attained increased with the activation voltage. At mean membrane potentials negative to −82 mV, or when quiescent intervals were less than 30 sec, the ability to induce triggered activity diminished abruptly. At mean potentials positive to about −72 mV, or
when quiescence was longer than about 2½ min, there was no further significant shortening in the cycle length of the triggered activity. As mentioned previously, other factors in addition to the decay of membrane potential may be involved here. To ensure that these effects of the duration of quiescence did not confuse our results, all episodes of triggered activity were separated by at least 2½ min of quiescence.

The sequence of changes in the maximum diastolic potential of the tracing in the top panel of figure 8 is typical of that seen in all of the preparations we studied during episodes of triggered activity. As the triggered rhythm increased in rate, the maximum diastolic potential initially decreased. However, as the episode progressed, hyperpolarization again occurred so that the maximum diastolic potential after the terminal beat was typically the highest potential of the rhythm.

Effect of pacing on triggered rhythms. Of 38 preparations demonstrating prolonged triggered activity, 18 (47%) began with initial episodes of at least 5 min duration. We used these preparations to evaluate the response to pacing. The first intervention was over-

![Graph](attachment:image.png)

**FIGURE 6.** Effect of premature stimuli on triggered activity. Top, From the data derived at a basic drive cycle length of 1000 msec, the proportion of trials at each S₂ coupling interval that induced triggered activity was determined for each preparation. Triggering frequency was defined as the mean of these values from all preparations. The slope is significant (p < .01, n = 11). Bottom, The response of the coupling interval of the first triggered beat to variation of the coupling interval of the S₂ in those preparations that triggered (n = 5).

drive pacing for 15, 30, 60, and 120 beats at drive cycle lengths equal to 75% and 50% of the triggered cycle length in varied sequence. The results of overdrive pacing in 12 preparations are presented in figure 9. Because there were insignificant differences between the effects of overdrive for 15 and 30 beats, these two trials were combined. For the same reason, the trials of 60 and 120 overdrive beats also were combined. The left panel of figure 9 demonstrates that long periods of overdrive are more effective than short periods in terminating this rhythm. Moreover, the ratio of abrupt terminations to delayed terminations increases with the duration of overdrive. In the right panel of figure 9, overdrive trials were grouped by their cycle lengths, which were either 75% or 50% of the triggered cycle length. At shorter overdrive durations the two cycle lengths gave similar results, but at longer overdrive durations the shorter cycle length was more effective in terminating the rhythm.

In those instances in which at least one triggered beat followed the last beat of overdrive, we measured the escape interval from the upstroke of the last driven beat to the upstroke of the next triggered beat. This escape interval showed a linear relationship to the preceding overdrive cycle length (figure 10). As a result, when the overdrive cycle length was short (50% of the triggered cycle length), the escape interval also was short. The mean corrected escape interval in this instance was 0.82 ± 0.03, indicating overdrive accel-

![Graph](attachment:image.png)

**FIGURE 7.** Four examples of rate contour recordings from a tachometer circuit that displays beat-to-beat cycle length on the vertical axis vs time on the horizontal. Each example begins with several stimulated beats at a constant cycle length followed by an episode of prolonged triggered activity. The first triggered beat in each example is marked by an arrow.
The drive. Acceleration drive termination. Delayed afterdepolarization. Abrupt terminations typically occurred after very premature S2 (≤160 msec) when the S2 coupling interval approximated the effective refractory period of the preceding triggered beat, resulting in a depressed response to the S2. These terminations were reproducible after 60% of the trials at the same S2 coupling interval. In contrast, delayed terminations occurred in nine of 14 preparations, over the entire range of S2 coupling intervals, and were never reproducible at the same coupling interval.

The effects of premature stimulation on the return cycle length of triggered rhythms is reviewed in figure 11. The top panel shows a representative scatter plot of the corrected return cycle lengths from one preparation, graphed as a function of the corrected S2 coupling interval. As the corrected S2 coupling interval decreased to approximately 0.4 (corresponding to an actual S2 coupling interval of 160 msec in this example) and the response to the S2 became depressed, there was a sudden prolongation of the return cycle length. At S2 coupling intervals shorter than this, the premature impulse had virtually no effect on the intrinsic rhythm (the corrected return cycle length falls on line B in figure 11).
FIGURE 9. Efficacy of overdrive pacing in terminating established triggered rhythms. **Left**, The proportion of trials resulting in different types of termination events after overdrive pacing of short duration (15 to 30 beats) and long duration (60 to 120 beats) was determined for each preparation. The mean frequency of termination was then derived from these values. **Abrupt** terminations were those in which no triggered beats followed the cessation of the overdrive. **Delayed** terminations were those in which 1 to 30 triggered beats followed the overdrive. The bar labeled **Both** represents all terminations. (**p < .05, **p < .01, n = 12**). **Right**, The frequency of both types of terminations after overdrive at cycle lengths of 75% and 50% of the preceding triggered cycle length. (**p < .05, n = 10**).

To summarize the behavior of the return cycle length after **S2** at coupling intervals of 160 msec or longer, the data from each preparation were reduced by linear regression to a representative line. The scatter of raw data points about each regression line did not exceed the limits of ± 0.1 unit on the vertical scale. Eleven of 14 preparations showed a significant decrease of the return cycle length in response to a decrease of the **S2** coupling interval (p < .01), whereas three showed reset of the preceding triggered cycle length. Eight representative regressions are shown in the bottom panel of figure 11, only one of which has no significant slope.

**Discussion**

Comparison of triggered activity in coronary sinus to triggered activity in digitalis-toxic Purkinje fibers. The characteristics we have described for this model of triggered activity differ in several aspects from the behavior of triggered activity previously described in digitalis-toxic Purkinje fibers. The first important difference is that digitalis-toxic Purkinje fibers produce two or more delayed afterdepolarizations, whereas catecholamine-treated coronary sinus preparations typically have only one. Although the coronary sinus...
can rarely produce a second afterdepolarization, its amplitude is always small compared to that of the first, and we have never seen triggered activity initiated by it. In Purkinje fibers, on the other hand, triggered activity initiated by the second delayed afterdepolarization is the rule at basic drive cycle lengths of 400 msec or less.\textsuperscript{5,23} As a result of this, an analysis of the coupling interval of the first triggered beat generated by Purkinje fibers gives two distinct curves when expressed as a function of basic drive cycle length. One curve is representative of triggering by the first delayed afterdepolarization and the other by the second delayed afterdepolarization.\textsuperscript{5} The same relationship in the coronary sinus, however, is described by one continuous curve, corresponding to triggering by one delayed afterdepolarization only.

Additional differences exist in the case of triggered activity initiated by the combination of basic drive and premature stimulation. The cycle length of the first triggered beat after an S\textsubscript{2} in digitalis-superfused Purkinje fibers is described by a complex relationship wherein it can be either directly or inversely related to the S\textsubscript{2} coupling interval, depending on whether the first or second delayed afterdepolarization caused the triggered activity.\textsuperscript{5} In atrial fibers of the coronary sinus, however, the cycle length of the first triggered beat after an S\textsubscript{2} is independent of the degree of prematurity of the S\textsubscript{2}, reflecting the behavior of the single delayed afterdepolarization.

It is a widely held maxim that the rate of triggered rhythms increases as the initiating drive cycle length decreases. This relationship was reported for digitalis-superfused Purkinje fibers.\textsuperscript{5} In the coronary sinus model, however, it is clear that this relationship holds only for the first triggered beat. Both the minimum triggered cycle length and the equilibrium triggered cycle length are independent of the initiating drive.

In established triggered rhythms, the response to pacing interventions in these two models of triggered activity is somewhat different as well. After S\textsubscript{2} stimulation, the escape interval resets the preceding triggered cycle length in digitalis-superfused Purkinje fibers, and the relationship of the corrected return cycle length to the corrected S\textsubscript{2} coupling interval is apparently flat.\textsuperscript{5} In coronary sinus, however, the corrected return cycle length after an S\textsubscript{2} commonly increases as the corrected S\textsubscript{2} interval increases. Termination of the triggered rhythm by S\textsubscript{2} stimuli can occur in both models but appears to occur more frequently in atrial fibers of the coronary sinus.

After overdrive pacing, the characteristics of the escape interval are comparable in the two models, being directly related to the cycle length of the overdrive. In addition, both models showed an inverse relationship between the cycle length of overdrive and the frequency of termination. In the coronary sinus, however, triggered rhythms were more effectively terminated by longer periods of overdrive than by shorter ones, whereas in digitalis-superfused Purkinje fibers there was no correlation between the duration of overdrive (15 to 60 sec) and the ability to terminate the rhythm.\textsuperscript{5} The ratio of abrupt to delayed terminations is comparable in these two models of triggered activity.

**Application of the present findings to rhythms in the intact heart.** A typical triggered rhythm of the type we have described might be identified by the following characteristics: It should occur more readily at rapid underlying heart rates or as a result of rapid pacing. Premature impulses, either intrinsic or paced, should be more effective in its induction than the underlying basic rhythm, and the more premature the impulse, the more effective it should be.

Once triggered activity is induced, the coupling interval of the first triggered beat should be directly related to the cycle length of the initiating rhythm. When the triggered activity is induced by a premature impulse, the premature coupling interval should have little influence over the coupling interval of the first triggered beat. Triggered rhythms of this type should follow one of the rate contours presented in figure 7, most commonly increasing in rate to a characteristic steady state (which is independent of the cycle length of the initiating rhythm but may show some variation with changing conditions) and eventually slowing before termination. These rhythms should tend to terminate after overdrive pacing, with long periods of overdrive at short cycle lengths being most effective in inducing termination. The termination of the rhythm may be abrupt after cessation of the drive, or afterbeats may occur, gradually slowing in rate until final termination. When the rhythm persists after overdrive, the first escape cycle length should be directly related to the cycle length of the overdrive itself and should show overdrive acceleration (when the overdrive is approximately twice the rate of the intrinsic rhythm). Single premature stimuli over a wide range of coupling intervals should also terminate the rhythm. Return cycle lengths after premature impulses should typically have a slightly positive slope in relationship to the premature coupling interval. Unfortunately, the characteristics are not sufficiently specific to differentiate a triggered rhythm arising in coronary sinus from other mechanisms.

In describing these characteristics we are referring
to an artificial situation, wherein the environment is carefully controlled. However, the behavior of arrhythmias in the intact heart may be complicated by changes in the environment that are not readily monitored. One important factor in the behavior of triggered activity is membrane potential. Variations in membrane potential may occur as a result of a change in the frequency of stimulation of a site generating delayed afterdepolarizations. For example, partial entry block would result in infrequent stimulation of a site and a decrease in membrane potential, which in turn should tend to increase afterdepolarization amplitude and the frequency of triggering. In addition, the rate of triggered rhythms, once initiated, would vary depending on the membrane potential or duration of quiescence that preceded them. Membrane potential alterations resulting from factors other than stimulation frequency (e.g., accumulation of K+ in the cellular clefts) might contribute to these effects as well. Another important variable is the availability of catecholamines. As endogenous levels of catecholamines (either circulating or neurally released) vary, so would the amplitude of the afterdepolarizations, the frequency of triggering, and the rate of triggered rhythms.

Another question to ask is why the arrhythmias we demonstrated in the coronary sinus model do not appear to occur frequently in vivo. In dealing with this question we first considered the fact that to induce delayed afterdepolarizations alone required the addition of $5 \times 10^{-8}$M to $2 \times 10^{-6}$M epinephrine and to induce triggered activity consistently required concentrations as high as $1 \times 10^{-5}$M. We are not aware of the concentrations of norepinephrine released by sympathetic terminals in the coronary sinus. Whether or not cleft concentrations of norepinephrine sufficient to have an agonist effect equivalent to that of the epinephrine superfused in these studies is unknown. Even if the appropriate concentration is attained, there is another difference between our preparation and the coronary sinus in situ. That is, cells in the former are coupled to other atrial cells, which might tend electronically to inhibit depolarization or delayed afterdepolarizations during phase 4. In contrast, we are working with a small, completely isolated and thereby uncoupled tissue. It may be that in the heart in situ some protection via entry block of the coronary sinus fibers is needed to uncouple them so that the catecholamine effect can then be expressed. That this may well be the case was demonstrated by Wit et al. In conclusion, when considering the identification of triggered activity in the intact heart, comparison of the present results to those obtained with digitalis suggests that no single and invariant set of rules characterizing these two types of triggered activity is applicable. Rather, these different types of triggered activity have some similar and some different characteristics, which will complicate our attempts to identify them, especially when using pacing techniques alone in intact systems.

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