The response to overdrive pacing of triggered atrial and ventricular arrhythmias in the canine heart

GABRIELLA MALFATTO M.D., TOVE S. ROSEN, M.D., AND MICHAEL R. ROSEN, M.D.

ABSTRACT Although triggered activity has been identified in isolated atrial tissue with the use of cellular electrophysiologic techniques, there has been no identification of triggered atrial arrhythmias in situ. Moreover, it is unclear whether triggered rhythms of different causes and sites of origin in the heart exhibit uniform responses to pacing that might aid in their identification. We therefore studied arrhythmias induced by overdrive pacing in three canine preparations, and based the analysis of our results on guidelines derived from microelectrode studies. We studied ventricular tachycardias induced by ouabain or by anterior wall myocardial infarction and atrial (coronary sinus) arrhythmias induced by the infusion of epinephrine into the great cardiac vein. In the ouabain and postinfarction preparations, right ventricular epicardial pacing induced ventricular premature beats or tachycardias whose recovery intervals after cessation of pacing shortened and showed overdrive acceleration as pacing rate increased. The first postspacing beat displayed progressive fusion with the paced beats but transient entrainment could not be induced. In the coronary sinus, the recovery intervals of impulses induced by epinephrine and pacing decreased as the drive rate increased, and inducibility of the paced rhythms increased at faster drive rates. Thus, the recovery intervals of triggered activity induced in the coronary sinus are phenomenologically similar to those of infarction-induced triggered rhythms. This is the first demonstration of consistent behavior in response to pacing of diverse types of triggered activity. Considered in light of the failure to induce transient entrainment, the results emphasize the potential utility of pacing in clinical identification of triggered rhythms and their differentiation from reentry. Circulation 77, No. 5, 1139–1148, 1988.

ALTHOUGH much has been done to characterize delayed afterdepolarization-induced triggered rhythms in isolated cardiac tissues and in intact animals, it remains difficult to identify triggered arrhythmias clinically and to distinguish them from reentry. The cellular electrophysiologic “rules” that have been applied to the identification of triggered rhythms in the intact heart are derived largely from studies of digitalis-toxic Purkinje fibers. However, delayed afterdepolarizations are inducible in settings other than digitalis toxicity, and experimental evidence suggests that not all triggered activity responds to pacing in the same fashion. We have reviewed the basis for these statements in detail; the following is a brief example. Ouabain superfusion of Purkinje fibers usually induces two or more delayed afterdepolarizations. Each of these shows a linear decrease in the relationship of its coupling interval to the drive cycle length of a preparation as drive cycle length is decreased. The first in a sequence of triggered beats induced by an afterdepolarization shows the same linear coupling interval relationship, and subsequent triggered beats tend to increase in rate as the preceding drive rate increases. A complicating factor is that depending on whether a triggered rhythm is induced by the first or second delayed afterdepolarization in a sequence, the slope of the line relating its coupling interval to the basic drive will differ, and this can destroy the simple linear relationship one might expect in relating a triggered rhythm to the preceding drive period.

In contrast, delayed afterdepolarizations induced by catecholamine superfusion of the coronary sinus tend to occur singly, and the relationship of coupling interval to drive cycle length of an afterdepolarization (and the triggered beat it induces) is described by a single line. However, the voltage sensitivity of coronary sinus afterdepolarizations is sufficiently great that one might expect variations in the amplitude and coupling interval of afterdepolarizations to occur readily as drive rate and membrane potential change, potentially upsetting the
linear relationship expected for the drive rate and the coupling interval of the triggered action potential. Finally, in contrast to digitalis-induced triggered rhythms, those in coronary sinus show a linear relationship with drive rate for the first triggered beat only; subsequent beats tend to decay back to the rate of the initial rhythm that occurred before pacing.

Observations such as the above led us to ask whether any of the descriptors of triggered rhythms that are seen at the cellular level might rationally be applied to the study of clinical arrhythmias. We therefore decided to study three preparations of triggered rhythms in intact animals: that induced by digitalis, which induces more than one delayed afterdepolarization in the proximal Purkinje system and which we considered a standard; that occurring 24 to 72 hr after coronary artery ligation, which tends to induce single afterdepolarizations in subendocardial Purkinje fibers; and that induced by catecholamines in the coronary sinus. The study of the coronary sinus required that we develop a new preparation, since there has been no description of atrial arrhythmias induced by triggered mechanisms in situ. Finally, because transient entrainment has been described as a means for distinguishing reentrant from other arrhythmogenic mechanisms, and because the distinction between triggered and reentrant mechanisms based on the response to pacing is a difficult one, we tested whether the rules described for transient entrainment might be met by triggered activity.

Methods

We studied digitalis-induced ventricular arrhythmias and catecholamine-induced coronary sinus arrhythmias in anesthetized dogs and infract-induced arrhythmias in conscious dogs.

Preparation of animals for studies of digitalis-induced ventricular arrhythmias and catecholamine-induced coronary sinus arrhythmias. We anesthetized mongrel dogs of both sexes (15 to 20 kg) with 30 mg/kg iv pentobarbital and intubated and artificially ventilated them. Supplemental doses of 1 to 2 mg/kg iv pentobarbital were given as needed (approximately every 2 hr). A right lateral thoracotomy was performed in the fourth intercostal space of each dog, and the heart was exposed and suspended in a pericardial cradle.

For the study of digitalis-induced arrhythmias, we sutured two bipolar plaque electrodes to the epicardium of the anterolateral right ventricle and the right outflow tract. For the study of catecholamine-induced coronary sinus arrhythmias, we sewed two similar electrodes to the epicardium of the right atrium, one in the sinus node region, the other to the epicardium overlying the ostium of the coronary sinus. A 20-gauge cannula was inserted into the great cardiac vein near its junction with the coronary sinus and was threaded retrogradely through the lumen for a distance of about 2 cm, and then a slow infusion of physiologic saline was started through the cannula. In some dogs, we placed an additional cannula in the right atrial appendage, secured it with a purse string, and infused saline via this route as well. We checked the position of the coronary sinus cannula at the end of each experiment by incising the right atrium to expose its endocardial surface and then incising and opening the coronary sinus from the endocardium.

For all animals, the electrocardiogram and at least one ventricular or atrial electrogram was continuously displayed and data were stored by means of an electrostatic recorder at paper speeds varying from 10 to 250 mm/sec. Blood pH, P02, and PCO2, and epicardial temperature were also monitored and maintained in the physiologic range.

Preparation of animals for studies of infract-induced arrhythmias. We anesthetized, intubated, and ventilated the dogs as above. Under sterile conditions, the left anterior descending coronary artery was isolated via a thoracotomy in the fourth left intercostal space, and was ligated in two stages. Bipolar electrodes were then sewed to the left atrial appendage and the left ventricular wall, as described previously. The dogs recovered from anesthesia and an ECG was recorded 24, 48, and in some instances 72 hr after the myocardial infarction while the animals stood quietly in a sling.

Protocols. We used the same pacing protocol for all studies: a programmable stimulator (Bloom) delivered rectangular pulses 2.5 to 3.0 msec in duration and twice the diastolic threshold through the atrial or ventricular electrodes or both, according to the needs of the experimental protocol. We performed sustained overdrive pacing at 15 to 20 sec, starting with a cycle length 5% shorter than the spontaneous sinus or ectopic cycle length and reduced the pacing cycle length in 20 msec decrements until a 1:1 relationship between stimulus and response no longer was seen (usually at a cycle length between 200 and 160 msec). We chose the 15 to 20 sec interval because prior studies have showed that delayed afterdepolarizations reach and maintain their peak amplitude after 5 to 15 paced beats, and hence, we were ensuring a steady state for the range of cycle lengths tested. After each trial, the basic cardiac cycle length returned to control values in about 20 sec. Nonetheless, the pacing trials were separated by intervals of at least 1 min.

In the study of digitalis-induced arrhythmias, we paced the heart through the electrode on the right ventricular outflow tract. After control pacing during sinus rhythm, we injected 30 to 40 μg/kg ouabain slowly. We performed the pacing protocol 30 min after drug administration, at which time a stable electrocardiographic pattern was present. We then injected an additional 30 to 40 μg/kg of ouabain and repeated the pacing protocol.

In the study of catecholamine-induced coronary sinus arrhythmias, we first paced from the electrode opposed to the coronary sinus and recorded the P wave morphology (figure 1). For purposes of comparison we also paced from the right atrial electrode near the sinus node. After a control trial of pacing from the right atrial electrode, epinephrine was infused into the coronary sinus (1.0, 2.0, and 4.0 μg/kg/min, for 10 min each) and the pacing protocol was repeated at the end of each period. After a 90 min washout, we infused epinephrine directly into the right atrium of some dogs and repeated the pacing protocol.

In the study of myocardial infarction, we paced the left atrium and the left ventricle simultaneously: the resultant overdrive suppression of the sinus node pacemaker facilitated our measurement of the ventricular recovery cycle length.

Data analysis. We averaged the cycle length of the spontaneous rhythm (atrial and/or ventricular) during control conditions for the 20 beats preceding each pacing run. The recovery cycle length was measured from the last paced to the first spontaneous QRS complex at a paper speed of 250 mm/sec. To account for the variability in the spontaneous sinus or ventricular rhythm, we normalized both the pacing cycle length and the recovery intervals and expressed them as a fraction of the average spontaneous cycle length. For every experiment we then considered five ranges of normalized pacing cycle length: 0.45 to 0.55, 0.55 to 0.65, 0.65 to 0.75, 0.75 to 0.85, and 0.85 to 0.95.
For each range, we obtained normalized recovery intervals by averaging the results of three to four trials and subsequently related them to the normalized pacing cycle length at which they had been obtained. We also studied the morphology and the cycle length of 1 to 20 beats after the cessation of pacing.

We considered an impulse to originate from the coronary sinus region when its P wave had the same morphology observed during preliminary pacing of the coronary sinus region and it was accompanied by changes in the sequence of atrial electrograms consistent with an origin in the coronary sinus region.

To evaluate the frequency of induction of ectopic activity by pacing, we first considered the percentage of trials resulting in ectopic activity in each experiment within a given range of normalized pacing cycle lengths. We then averaged these percentages across all the experiments to give the mean induction frequency corresponding to each range of normalized pacing cycle lengths.

Statistical analysis. Data are expressed as the mean ± SEM. The curves relating the mean normalized recovery intervals to the normalized pacing cycle length were analyzed by analysis of variance (ANOVA) and Scheffé’s test was performed whenever appropriate.23 The mean frequencies of induction of ectopic activity from the coronary sinus region were calculated as stated above and compared by ANOVA after an arcsine transformation was performed to bring the variance of data near the extremes of 0% and 100% closer to the variance near 50% on the proportional scale.23 A p < .05 was considered indicative of a significant difference.

Results

Digitalis-induced arrhythmias. We administered 30 to 40 μg/kg ouabain to eight anesthetized dogs. In two a stable ventricular tachycardia appeared after 10 min: these animals were not given a second dose of ouabain. Sinus rhythm persisted in the remaining six dogs. We performed ventricular pacing in these six dogs in an attempt to induce ectopic activity, and then gave them an additional 30 to 40 μg/kg dose of ouabain. Two dogs remained in sinus rhythm and the other four developed ventricular tachycardia. These four plus the two that had developed ventricular tachycardia after one dose of

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac rhythm and RR intervals in digitalis experiments</td>
</tr>
<tr>
<td>Ouabain dose</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td><strong>Basic rhythm</strong></td>
</tr>
<tr>
<td>RR (msec)</td>
</tr>
</tbody>
</table>

NSR = normal sinus rhythm; VT = ventricular tachycardia.
ouabain composd the group in which the effects of pacing on sustained ventricular tachycardia were studied.

We therefore studied six dogs in sinus rhythm after a nontoxic dose of ouabain and six dogs with a digitalis-induced ventricular tachycardia (table 1). Four animals were studied under both conditions. During the control period, there was overdrive suppression of sinus rhythm after ventricular pacing in all animals. In the six dogs still in sinus rhythm after the first ouabain injection, pacing induced isolated ventricular premature beats at a normalized pacing cycle length of 0.85 to 0.95 and brief runs of monomorphic ventricular tachycardia at a normalized pacing cycle length less than 0.75. The recovery intervals of the ventricular beats and of the tachycardia shortened as the pacing cycle length decreased (423 ± 7 msec at a normalized pacing cycle length of 0.85 to 0.95 vs 339 ± 17 msec at a normalized pacing cycle length of 0.45 to 0.55, p < .05) and overdrive acceleration was evident after very fast pacing (normalized recovery cycle length of 0.91 ± 0.02, with a spontaneous cycle length of 402 ± 21 msec after pacing at a normalized cycle length of 0.45 to 0.55) (figure 2). In three dogs with ventricular tachycardia, the first beat of the induced tachycardia (which was of 3 to 20 beats duration) assumed a morphology similar to that of the paced beats as the drive cycle length was decreased. The succeeding beats always returned to the morphology of the original ventricular tachycardia.

The cycle lengths of successive beats in the induced ventricular tachycardias are shown in figure 3. Their cycle lengths shortened gradually after pacing at a normalized cycle length of 0.65 to 0.75 and irregularly after pacing at a shorter cycle length (0.45 to 0.55). The final, steady-state cycle lengths did not differ in the two groups (375 ± 31 msec after pacing at a normalized cycle length of 0.45 to 0.55 and 373 ± 67 msec after pacing at a normalized cycle length of 0.65 to 0.75) and were shorter than the sinus cycle length (402 ± 21 msec).

In the six dogs with digitalis-induced ventricular tachycardia we obtained results analogous to those described above. The normalized recovery intervals decreased at faster pacing rates (362 ± 8 msec at a normalized pacing cycle length of 0.85 to 0.95 vs 309 ± 15 msec at a normalized pacing cycle length of 0.45 to 0.55, p < .05), and showed overdrive enhancement after pacing at a short cycle length (normalized recov-

![Figure 2](http://circ.ahajournals.org/)

**FIGURE 2.** Relationship between the normalized recovery cycle length and the normalized pacing cycle length in the digitalis experiments. There was overdrive suppression of the sinus rhythm observed during control (circles; n = 8). Pacing induced ventricular ectopic activity after the first ouabain dose (unfilled squares; n = 6) and did not interrupt the ventricular tachycardia after the second ouabain dose (filled squares, n = 6). The normalized recovery intervals became progressively shorter with progressively faster pacing and overdrive acceleration was eventually observed. *p < .05 compared with values at 0.85 to 0.95.

![Figure 3](http://circ.ahajournals.org/)

**FIGURE 3.** Cycle lengths of successive beats after the cessation of pacing in dogs in sinus rhythm with pacing-induced ventricular tachycardia after the first ouabain dose (unfilled circles; n = 6) and in dogs with stable monomorphic ventricular tachycardia after the second ouabain dose (filled circles, n = 5). The triangles on the left of each panel indicate the cycle lengths of the ventricular tachycardia and the sinus rhythm. Two ranges of pacing cycle length are presented. The postpacing rhythm accelerated in both situations and was more irregular for some beats after fast pacing. The final rate attained in both instances was similar. *p < .05 vs first postpacing beat. *p < .05 vs basic rhythm.
ally the second, recovery beat showed variable degrees of fusion, but never at a coupling interval equaling the paced rate as should have been the case if the ventricular tachycardia were "entrained."

Catecholamine-induced coronary sinus arrhythmias. We studied nine dogs, in seven of which we cannulated the great cardiac vein, and in two of which we also inserted a right atrial cannula. In the other two we used only a right atrial cannula. Table 2 shows the RR intervals for sinus rhythm during the control period and during epinephrine infusion, through which sinus rhythm persisted. During control, pacing always overdrive suppressed the sinus rhythm. During epinephrine infusion (table 2) we never observed ectopic activity from the coronary sinus, the atria, or ventricles. However, in six of seven dogs, pacing induced ectopic activity originating from the coronary sinus and demonstrating fusion with the sinus P wave (figure 5).

This ectopic activity was more easily induced by fast pacing (58% of trials at a normalized pacing cycle length of 0.45 to 0.55 vs 31% of trials at a normalized pacing cycle length of 0.85 to 0.95, p < .05) (figure 6). The duration of the bursts of ectopic activity was 7 ± 1 beats and was not influenced by the pacing cycle length or by the epinephrine concentration. We calculated the relationship between the normalized recovery intervals and the normalized pacing cycle length in five dogs in which ectopic activity was present after almost all the pacing trials. These two variables had a significant relationship (figure 7), with a progressive shortening of the recovery interval (from 443 ± 19 msec at a normalized pacing cycle length of 0.85 to 0.95 to 320 ± 32 msec at a normalized pacing cycle length of 0.45 to 0.55, p < .05), and overdrive acceleration after fast pacing (normalized recovery interval of 0.85 ± 0.11 and cycle length of 359 ± 19 msec after pacing at a normalized cycle length of 0.45 to 0.55). We calculated the cycle length of successive impulses during the induced ectopic activity in the same five dogs. As shown in figure 8, the rhythm was irregular for 2 to 3 beats and then gradually slowed, attaining a stable cycle length that was not influenced by the preceding

![Figure 4](http://circ.ahajournals.org/)

**FIGURE 4.** Gradual shift in the morphology of the first postpacing beat during progressive shortening of pacing cycle length in a dog with ouabain-induced ventricular tachycardia. The basic morphology is shown in the top panel. The other panels indicate the pacing cycle length, the last paced beat (dot), and the recovery beat at various pacing cycle lengths. See text for discussion.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Cardiac rhythm and RR intervals in coronary sinus experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Epi dose in CS (μg/kg/min)</td>
</tr>
<tr>
<td></td>
<td>Control (n = 9)</td>
</tr>
<tr>
<td>Basic rhythm</td>
<td>NSR</td>
</tr>
<tr>
<td>RR (msec)</td>
<td>417 ± 15</td>
</tr>
</tbody>
</table>

NSR = normal sinus rhythm; VT = ventricular tachycardia; CS = coronary sinus; RA = right atrium; Epi = epinephrine.
pacing cycle length. For example, it was $432 \pm 17$ msec after pacing at a normalized cycle length of 0.65 to 0.75 and $410 \pm 10$ msec after pacing at a normalized cycle length of 0.45 to 0.55 ($p > .05$). The ectopic activity then was suppressed by sinus rhythm super-

INDUCTION

![Figure 5](image_url)

**Figure 5.** Induction of ectopic activity from the coronary sinus. A. Pacing the atrium at two different cycle lengths led to slight overdrive suppression of the sinus rhythm. B. During the infusion of epinephrine (2.0 μg/kg/min) into the coronary sinus, pacing of the atrium was followed by a series of ectopic beats. Notice the different P wave and the different pattern of activation in the electrogram from the coronary sinus region, indicating the different origin of these beats. The bottom panel illustrates the fusion between the coronary sinus and normal sinus P waves (fifth beat from right).

pacing at a shorter cycle length ($360 \pm 15$ msec). The infusion of epinephrine into the right atrium did not significantly modify the mean RR interval (Table 2), nor did pacing induce atrial ectopic activity with the characteristics described above for the coronary sinus. Overdrive suppression of sinus rhythm was always observed (figure 7). In two dogs, a repeat epinephrine infusion was given via the atrium after an infusion to the great cardiac vein. As shown in figure 9, only during coronary sinus infusion was ectopic activity initiated in the coronary sinus region.

**Myocardial infarction-induced arrhythmias.** We produced myocardial infarction in seven dogs. Table 3 shows the control RR values for the ventricular tachycardia and for sinus rhythm at 24, 48, and 72 hr after coronary ligation. At 24 hr, five dogs had stable ventricular tachycardia (polymorphic in three and monomorphic in two) and two were in sinus rhythm with frequent ventricular premature beats. In the former, the normalized recovery intervals after pacing showed neither overdrive suppression nor acceleration (figure 10, left). In the two dogs in sinus rhythm, pacing was followed by bursts of ventricular tachycardia (3 to 10 beats), the recovery intervals of which shortened significantly as pacing became faster (from a mean of 527 msec at a normalized pacing cycle length of 0.85 to 0.95 to 437 msec at a normalized pacing cycle length of 0.45 to 0.55). Overdrive acceleration was demonstrable: the normalized recovery interval was 0.96 at

![Figure 6](image_url)

**Figure 6.** Percent induction of ectopic activity from the coronary sinus region of six dogs. Left, curves obtained during the infusion of epinephrine at various concentrations. No differences were seen among these curves. The pooled data are shown on the right: ectopic activity occurred more frequently after rapid pacing. * $p < .05$ vs value at 0.45 to 0.55.
a basic sinus cycle length of 458 ± 13 msec after pacing at a normalized cycle length of 0.45 to 0.55.

Forty-eight hours after infarction, all dogs were in sinus rhythm with rare ventricular premature beats. In all of them, rapid pacing (normalized cycle length 0.45 to 0.55) induced ventricular ectopic activity (premature beats or tachycardia). However, in only three was pacing consistently followed by ventricular premature beats or salvos of tachycardia after all pacing trials, thus allowing us to correlate the recovery intervals with the different pacing cycle lengths. In these three dogs, we observed a significant reduction in the normalized recovery cycle length (459 ± 38 msec at a normalized pacing cycle length of 0.45 to 0.55 vs 592 ± 20 msec at a normalized pacing cycle length of 0.85 to 0.95, p < .05), as well as overdrive acceleration with a reduction in pacing cycle length (normalized recovery interval of 0.90 ± 0.08 with a cycle length of 508 ± 24 msec after pacing at a normalized cycle length of 0.45 to 0.55) (figure 10, middle). Seventy-two hours after infarction, these three dogs displayed only overdrive-suppressible sinus rhythm (figure 10, right).

**Discussion**

We view the present studies as important for three reasons: first, cellular electrophysiologic data to date have shown sufficient heterogeneity in the response of delayed afterdepolarizations and triggered activity to pacing to raise some concern over the likelihood that
a uniformity of response is likely in the intact heart (for review, see Johnson and Rosen10). Second, although triggered activity has been hypothesized as a mechanism for atrial arrhythmias, it has not been demonstrated in situ, nor has its similarity to other forms of triggered activity been tested. Finally, investigators have suggested that “transient entrainment” of cardiac arrhythmias may be a specific descriptor of reentry,21, 22 yet the possibility that such entrainment might occur in a triggered rhythm has not been tested, although systematic changes in morphology of digitalis-induced triggered impulses have been described.10 To carry out our studies we reproduced two preparations that we and others have reported in the past, digitalis-induced9, 10, 24 and infarct-induced20, 25 ventricular tachycardia, and we developed a new preparation of catecholamine-induced coronary sinus tachycardia. All three preparations have cellular electrophysiologic counterparts that incorporate delayed afterdepolarizations and triggered activity.2–4, 6, 7, 17, 18, 20

We have demonstrated that arrhythmias arising under these different experimental conditions but assumed to be triggered in their origin display similar behavior after their induction or perturbation by brief periods of pacing. Considering the preparations individually, several prior studies support the hypothesis that triggered activity is, in fact, the mechanism for many digitalis-induced arrhythmias.13, 24, 26 These studies dealt either with arrhythmias induced by pacing in the absence of overt toxicity9 or those considered the result of digitalis toxicity.10, 25 We reproduced both situations in the same animals to observe possible differences between the two, as well as to compare their responses to those of coronary sinus and myocardial infarction arrhythmias. The responses to pacing of ventricular ectopic activity induced after doses of digitalis too small to induce stable tachyarrhythmias and doses that did not induce toxic arrhythmias did not differ substantially. As reported by Gorgels et al.,10 the first and occasionally the second postpacing beat gradually changed in morphology, becoming ever more similar to the paced beats. This can be explained by the fact that pacing may trigger ectopic impulses from more than one site in the ventricle, and that impulses from a locus close to the site of stimulation can fuse variably with the impulses generated by the dominant rhythm. It is unlikely that these fusion beats represent “transient entrainment,”21, 22 because their cycle lengths differed from the pacing cycle length; only the morphology of the paced beats persisted after pacing was terminated.

Our experiments demonstrated for the first time in vivo an atrial arrhythmia with the characteristics of triggered activity originating in the coronary sinus. This mechanism for coronary sinus arrhythmia has been postulated,1–7 but never proven. Studies in vitro have shown that superfusion of isolated coronary sinus preparations with high concentrations of epinephrine elicits delayed afterdepolarizations and triggered activity,7, 16 whereas we observed ectopic activity only when pacing was superimposed on epinephrine perfusion. These differences may be accounted for by electrotonic inhibition of the activity originating in the sinus, exerted by the surrounding atrial tissues in vivo, or by exit block of triggered activity from the coronary sinus region. Both these phenomena might be counteracted during the period of overdrive suppression of sinus node activity after pacing. Such phenomena may also explain why arrhythmias of the type we have observed are rather uncommon clinically and until now have been so difficult to reproduce experimentally.

![FIGURE 10. Relationship between the normalized recovery cycle length and the normalized pacing cycle length in dogs with myocardial infarction. Left, Twenty-four hours after infarction, five dogs were in ventricular tachycardia (unfilled circles) and two were in sinus rhythm (filled circles). In the latter, we induced ventricular tachycardia with pacing. Middle, Forty-eight hours after the infarct, all dogs were in sinus rhythm and ventricular tachycardia was inducible in three. Right, Seventy-two hours after infarction, the same three dogs had only an overdrive-suppressible sinus rhythm. * p < 0.5 vs 0.85 to 0.95.]

---

**TABLE 3**

<table>
<thead>
<tr>
<th>Cardiac rhythm and RR intervals in myocardial infarction experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT at 24 hr</td>
</tr>
<tr>
<td>(n=5)</td>
</tr>
<tr>
<td>RR</td>
</tr>
</tbody>
</table>

Abbreviations as in tables 1 and 2.1+7 Frequent ventricular premature beats.
One might argue that in the coronary sinus experiments, the ectopic activity might have originated from other subsidiary pacemakers in the lower right atrium. These are known to generate delayed afterdepolarizations and triggered activity in vitro during exposure to catecholamines. That such an atrial origin is unlikely is suggested by the fact that the infusion of epinephrine into the right atrium could have equally well reached these subsidiary atrial pacemakers; yet, atrial infusion of epinephrine always induced an overdrive-suppressible sinus rhythm.

The final example of triggered arrhythmias we investigated was that occurring after myocardial infarction. Arrhythmias 24 hr after ligation of the anterior descending coronary artery have been attributed to automaticity, triggered activity, or reentry. Recent studies have suggested that both abnormal automaticity and triggered activity may be the underlying mechanism, depending on experimental conditions. Our present results are consistent with this hypothesis. Five of the seven 24 hr arrhythmias showed continuing ectopic activity that was not overdrive suppressed (or minimally suppressed), a result consistent with automatic foci. In contrast, the two dogs in sinus rhythm 24 hr after infarction showed pacing-induced ventricular ectopic activity that behaved like triggered activity. These animals might have had smaller infarcts, a condition that may be accompanied by lesser membrane depolarization and more ready induction of triggered arrhythmias. The ventricular beats we observed 48 hr after infarction appeared to be triggered, as previously described. The subendocardium at this time has a higher membrane potential than at 24 hr and in this setting triggered arrhythmias are likely to appear.

A major aim of our study was to determine whether these animal preparations reflect that pattern of response to pacing predicted from microelectrode observations. In vitro, the occurrence of a triggered rhythm is facilitated by rapid pacing. This was evident in all of these preparations, although the frequency of occurrence at all cycle lengths was higher in the presence of digitalis toxicity. In vitro, the coupling interval of the first beat of a triggered rhythm is directly related to the pacing cycle length, with a tendency toward overdrive acceleration after fast pacing. This occurred consistently in our experiments (figures 2, 7, and 9). This was of interest because in digitalis-toxic Purkinje fibers (but not in coronary sinus fibers or Purkinje fibers from infarcted hearts), two or more delayed afterdepolarizations usually follow the discontinuation of pacing, and in the range of pacing cycle length analogous to that which we used, the second delayed afterdepolarization usually initiates triggered activity. Had this happened in our study, the normalized recovery intervals of both the induced and spontaneous ventricular arrhythmias in digitalis-treated dogs should have been longer than normalized recovery intervals in the coronary sinus and infarct preparation. This, however, never occurred. It is possible that in the intact animal, the activity of the sympathetic nervous system and of the circulating catecholamines might have increased the amplitude of the first digitalis-induced delayed afterdepolarization above threshold over the entire range of pacing cycle lengths used, as has been recently reported, so that it consistently reached the threshold for the induction of a triggered rhythm.

In the digitalis-treated dogs the rates of both the induced and the spontaneous ventricular tachycardias accelerated for a few beats after pacing, and were irregular after pacing at short cycle lengths (figure 3). In contrast, the rate of the ectopic activity from the coronary sinus decreased slightly after pacing (figure 8). These different behaviors parallel the differences between the triggered rhythms induced in ouabain-treated Purkinje fibers and in fibers from the coronary sinus during epinephrine superfusion, as has been discussed in detail.

In conclusion, the rules derived from experimental observations in vitro are uniform predictors of the behavior of the first postspacing beat of disparate types of triggered arrhythmia in vivo. In the intact animal, the similar behavior of the arrhythmias we induced with pacing is consistent with the hypothesis that their mechanism is a common one. The response to pacing can be considered indicative of triggered activity in the intact heart if a linear relationship is demonstrable between recovery cycle length for the first postspacing beat and the pacing cycle length of the arrhythmia. There are the following caveats, however: failure to see this relationship of cycle lengths does not indicate that the arrhythmia is not triggered, demonstration of this relationship in a setting that also shows transient extrastimulation favors the diagnosis of reentry, and finally, some automatic tachycardias occurring in depolarized cardiac fibers may demonstrate a similar linear relationship, although the slope tends to be shallower.

Hence, the techniques of overdrive pacing and observation of spontaneous variations in cycle length represent useful means for consideration of mechanism. However, more complex investigational techniques, like drug matrixes, monophasic action potential recordings, and mapping require continued ex-
ploration as means for accurate discrimination among mechanisms.

We are grateful to Dr. Irina Golyakhovsky for her assistance in performing certain of the experiments, to Sharon Miller for skilled technical assistance, and to Susan McMahon and Karen Liebert for carefully preparing the manuscript.

References
29. Friedman PL, Stewart JR, Wit AL: Spontaneous and induced cardiac arrhythmias in subendocardial Purkinje fibers surviving extensive myocardial infarction in dogs. Circ Res 33: 612, 1973

1148 CIRCULATION
The response to overdrive pacing of triggered atrial and ventricular arrhythmias in the canine heart.
G Malfatto, T S Rosen and M R Rosen

Circulation. 1988;77:1139-1148
doi: 10.1161/01.CIR.77.5.1139

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/77/5/1139

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at: http://circ.ahajournals.org/subscriptions/