In Vivo Induction of “Focal” Triggered Ventricular Arrhythmias and Responses to Overdrive Pacing in the Canine Heart

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Delayed afterdepolarizations and triggered activity were evoked in focal areas of myocardium in vivo by local exposure of endocardium to ouabain by means of a catheter electrode system capable of recording monophasic action potentials (MAPs) and delivering ouabain to the recording site. MAPs were recorded from the septum and the posterior wall of the left ventricle with silver–silver chloride electrode catheters. Ouabain (10⁻² M) was infused through the MAP recording catheter onto the endocardial surface of the septum. After infusion of 10 µg/kg ouabain, the amplitude of MAPs recorded from the septum (the site of ouabain infusion) decreased from 37.4±11.8 to 32.0±10.1 mV (p<0.01), MAP duration at 50% repolarization shortened from 160±29 to 148±34 msec (p<0.01), and MAP duration at 90% repolarization shortened from 198±38 to 189±46 msec (p<0.01). MAPs recorded from the posterior wall (the reference site) were unchanged. Delayed afterdepolarizations were recorded at the site of ouabain infusion, but not at the reference site, when the heart was paced at cycle lengths of 200–600 msec. Additional infusion of ouabain induced sustained monomorphic ventricular tachycardia (VT) (mean cycle length, 369±12 msec) in all 15 dogs studied. The mean concentration of ouabain required to induce VT was 20.9±10.0 µg/kg. Paced QRS complexes when stimulated at the site of ouabain infusion had the same morphology as those of spontaneous VT. Local perfusion of verapamil, 0.015–0.034 mg/kg, through the MAP recording catheter onto the site of ouabain infusion completely eliminated VT and premature ventricular contractions. After perfusion of verapamil, delayed afterdepolarizations could no longer be induced by pacing. These observations indicate that induced VT originated from the site of ouabain infusion, and the presence of delayed afterdepolarizations before development of VT strongly suggests that the induced VT was due to triggered activity. Using this model, we examined the responses to rapid ventricular pacing of “focal” triggered VT. The first beat of the reinitiated tachycardia displayed the same morphology as the spontaneous VT. The recovery interval of the first postpacing impulse decreased as the pacing cycle length shortened and demonstrated overdrive acceleration at a relatively short pacing cycle length (less than 65% of the original VT). The recovery interval of the first postpacing impulse was shorter when the pacing site was closer to the focus of the triggered arrhythmia. The coupling interval of the second postpacing impulse was slightly shorter than the recovery interval of the first postpacing impulse. It gradually lengthened after the second postpacing impulse and returned to the original VT cycle length at 7±1 impulses after cessation of pacing. Constant fusion only occurred at a pacing cycle length identical to that of the original VT, and thus, by definition, the arrhythmia could not have possibly been entrained. We conclude that the responses to overdrive pacing of focal triggered ventricular arrhythmias may be helpful in distinguishing this type of arrhythmia from arrhythmias due to reentry or due to global influences that may generate triggered activity. (Circulation 1990;82:549–559)
The ability to identify triggered arrhythmias and to distinguish them from reentrant arrhythmias to guide appropriate therapy would be clinically relevant. The response of clinical arrhythmias to overdrive pacing has been used for this purpose. During the past two decades, delayed afterdepolarizations and triggered activity have been well characterized in isolated cardiac tissues. In addition, responses of reentrant arrhythmias to overdrive pacing in vivo have been extensively studied and characterized by Waldo et al as "transient entrainment." However, little information is available on triggered arrhythmias occurring in vivo because of the lack of an appropriate, well-controlled in vivo model of triggered arrhythmias. Gorgels et al and Malfatto et al examined the responses of digitalis-induced arrhythmias to pacing in dogs. One of the distinctive features they found was that several postspacing beats displayed various morphologies of QRS complexes, because the pacing sites, as well as the intervening tissues, were exposed to drug and were susceptible to triggered activity. Triggered arrhythmias arising from small, limited areas of susceptible myocardium (focal triggered arrhythmias) may also play a role in clinical settings, such as the arrhythmias induced by acute or chronic ischemia or by reperfusion.

Malfatto et al studied triggered arrhythmias induced by anterior wall myocardial infarction. Although they reported the relation between the pacing cycle length and the recovery interval of the first postspacing impulse, they did not comment on the morphology of the reinitiated tachycardia after cессation of pacing. The development of various types of arrhythmias after myocardial infarction probably prevented such detailed analysis.

In the present study, we designed an in vivo model of focal triggered ventricular arrhythmias, in which we attempted to characterize the responses of delayed afterdepolarizations and ouabain-induced focal triggered arrhythmias to overdrive pacing.

Methods

Fifteen mongrel dogs of either sex, weighing 13–20 kg, were anesthetized with sodium pentobarbital (30 mg/kg i.v.) and ventilated with room air by a constant-volume respirator (model 600, Harvard Apparatus, South Natick, Mass.). Supplemental doses of 1–2 mg/kg pentobarbital i.v. were given as needed to maintain a constant level of anesthesia. Tidal volume and respiratory rate were adjusted to maintain blood gases and pH within the physiological range throughout the experiment. A heating pad was used to maintain a body temperature of 36±1°C. Saline-filled polyethylene catheters were placed in the right femoral artery to monitor arterial blood pressure and in the right brachial vein to infuse anesthetics and normal saline to replace spontaneous fluid losses. The fourth rib was removed on the left side, and the heart was exposed and suspended in a pericardial cradle. Teflon-coated stainless steel bipolar plunge electrodes (0.0015 in.) were placed through 22-gauge needles into the right ventricular (RV) outflow tract and apex, the left ventricular (LV) side of the intraventricular septum, and the LV anterior, lateral, and posterior free wall. The electrodes were used for stimulation and to record bipolar electrograms amplified through DC-coupled differential amplifiers (model DR-12, Electronics for Medicine, Pleasantville, N.Y.) at a frequency ranging from 30 to 500 Hz.

Recording of Monophasic Action Potentials

Silver–silver chloride contact electrode catheters permitted simultaneous recording of endocardial monophasic action potentials (MAPs) and local delivery of drugs to the recording site (Figure 1). The catheters were introduced through stab wounds in the LV free wall, and the recording tips were placed against the endocardial surfaces, one on the LV side of the intraventricular septum and the other on the posterior LV free wall. The catheters were secured by mechanical support. The recording pole of the electrode was approximately 1 mm in diameter, and the reference electrode was located 5 mm proximal to the recording end. The catheter had small holes immediately proximal to the recording pole through which normal Tyrode's solution or Tyrode's solution containing ouabain could be perfused. MAP signals were amplified by the DC-coupled differential amplifiers at a frequency ranging from 0.1 to 2,000 Hz. Throughout each experiment, MAPs were displayed simultaneously with other electrical signals and blood pressure on an oscilloscope (DR-12, Electronics for Medicine) and stored on a video cassette tape (SL-HF 900, Sony) for later analysis. Hard copy recordings were obtained on a chart recorder (model 220, Gould, Cleveland, Ohio).

Phases of the MAPs were defined according to standard definitions used for transmembrane action potentials. Amplitude was defined as the difference between phases 2 and 4; action potential duration was measured from the foot of the action potential to 50% (APD50) or 90% (APD90) repolarization. The measurements of the amplitude and coupling interval of delayed afterdepolarizations were made in a manner similar to those described by Rosen and Danilo. The amplitude was measured from the most negative level reached during repolarization to the peak positive level reached by the delayed afterdepolarizations. The coupling interval was defined as the interval between phase 0 of the action potential and the peak of the afterdepolarizations. The action potential parameters were measured with a computer program with analysis functions using a cursor moved at intervals of 0.5 msec.

The minimal acceptable amplitude of MAPs was 15 mV. Signals accepted for this protocol were stable for more than 1 hour without requiring any additional change in depth or position of the recording tip. Avoidance of artifacts during the diastolic phase of the action potential (phase 4), as described by Levine et al, was achieved by rigorous attention to recording stable resting potentials. In each experi-
ment, control MAPs were recorded continuously for at least 30 minutes to verify a stable baseline. If these criteria were not present, the recording site was changed to an adjacent site, and the experimental protocol was performed only when a constant shape of the MAPs and a stable resting potential were consistently recorded.

Experimental Protocol

MAPs were simultaneously recorded from the septum and the posterior wall. Tyrode’s solution was continuously perfused through the MAP recording catheter onto the septum at an infusion rate of 3 ml/min. After the 30-minute control recording, the stimulation protocol was performed, using rectangular pulses 1 msec in duration delivered at twice diastolic threshold with a programmable stimulator (model DTU, Bloom Associates, Narberth, Penn.). To obtain control data on delayed afterdepolarizations and triggered ventricular beats, a train of 19 stimuli was delivered to the RV outflow tract at pacing cycle lengths of 600–200 msec in 50–100-msec decrements. The stimulation protocol was repeated twice at each drive cycle length, separated by an interval of 30–60 seconds. We also performed pace mapping with electrode catheters placed on the septum and the posterior wall to compare the morphology of paced QRS complexes at the site of infusion to QRS complexes of ventricular tachycardia (VT). Trains of 19 beats of ventricular pacing impulses at cycle lengths of 400, 350, and 300 msec were introduced at both sites, and surface electrocardiographic leads I, II, III, aVR, aVL, aVF, and V1 were recorded.

After completion of the control protocol, the solution perfused through the septal electrode catheter
was changed to Tyrode's solution containing \( 10^{-5} \) M ouabain. After delivery of 10 \( \mu \)g/kg ouabain, the pacing protocol was repeated to examine the effects of pacing cycle lengths on the amplitudes and coupling intervals of delayed afterdepolarizations in dogs that had not yet developed sustained VT. Perfusion of ouabain was continued until a sustained VT developed. Whenever sustained VT developed and maintained a uniform morphology and constant cycle length, a train of 19 beats of rapid ventricular pacing was introduced from at least three stimulation sites. Rapid ventricular pacing was begun at a pacing cycle length of 10–20 msec longer than the VT cycle length and was shortened in 50-msec decrements until the VT was interrupted or the pacing cycle length reached 200 msec. The recovery interval of the first postpacing impulse was measured as the time interval between the last captured beat and the first spontaneous beat after cessation of pacing. The coupling interval of the second postpacing impulse was defined as the time interval between the first and second spontaneous beats after cessation of pacing; the coupling interval of subsequent postpacing impulses was defined similarly. All time intervals were measured at a paper speed of 125 mm/sec. To determine whether constant fusion and progressive fusion, criteria of transient entrainment for reentrant tachycardia,2–5 were present, we repeatedly scanned the pacing cycle length within a ±20-msec range of tachycardia cycle length in 2-msec decrements.

In four dogs, the effect of verapamil on VT was tested after completion of the pacing protocol. Verapamil hydrochloride (Sigma Chemical Co., St. Louis, Mo.), at a concentration of \( 10^{-4} \) M, was perfused through the septal electrode catheter at a rate of 3 ml/min. Drug-free Tyrode's solution was continuously perfused before perfusion of verapamil to exclude a simple washout effect with Tyrode's solution. When VTs or premature ventricular contractions (PVCs) were eliminated, the effect of verapamil on delayed afterdepolarizations and triggered ventricular beats was studied by delivering a train of 19 impulses from the RV outflow tract at pacing cycle lengths of 600–200 msec in 50–100-msec decrements.

**Statistical Analysis**

All data are presented as mean±SEM. Statistical significance was evaluated with the Student's paired or unpaired \( t \) test, where appropriate. Differences with a \( p \) value of less than 0.05 were considered significant.

**Results**

**Effect of Ouabain on Monophasic Action Potentials**

The characteristics of MAPs recorded from the septum and from the posterior wall in the control state and after infusion of 10 \( \mu \)g/kg ouabain are presented in Table 1. The characteristics of MAPs were compared during sinus rhythm. Sinus cycle length during the control state and after infusion of ouabain never differed by more than 50 msec in any of the dogs. In the control state, there were no significant differences between the amplitude, \( \text{APD}_{90} \), or \( \text{APD}_{90} \) of MAPs recorded from the septum and from the posterior wall. After infusion of 10 \( \mu \)g/kg ouabain, the amplitude of MAPs recorded from the septum decreased significantly, and the \( \text{APD}_{90} \) and \( \text{APD}_{90} \) were shortened compared with the control values. In the posterior wall, there were no significant changes in the amplitude, \( \text{APD}_{90} \), or \( \text{APD}_{90} \) after infusion of ouabain. Two dogs had developed sustained VT before the concentration of ouabain reached 10 \( \mu \)g/kg (3.9 and 6.0 \( \mu \)g/kg, respectively). The MAP changes induced by ouabain were similar to those observed in the other 13 dogs. However, the stimulation protocol for the induction of delayed afterdepolarizations could not be performed in these two dogs because of development of VT.

**Demonstration of Delayed Afterdepolarizations and Triggered Activity**

Trains of stimuli were delivered to the RV outflow tract after infusion of 10 \( \mu \)g/kg ouabain in the 13 dogs that had not developed sustained VT before completing the infusion of 10 \( \mu \)g/kg ouabain. Delayed afterdepolarizations were induced at the septal location in nine of 13 dogs (69%), whereas none of the dogs developed delayed afterdepolarization at any stimulation cycle lengths at the posterior wall site. In six of 13 dogs (46%), ventricular ectopic beats were induced at some, but not all, pacing cycle lengths. Figure 2 depicts an example of induced delayed afterdepolarizations (panel A) and an induced ectopic ventricular beat (panel B) when the RV outflow tract was paced repeatedly at a pacing cycle length of 300 msec. The ectopic beat occurred at the same coupling interval as the delayed afterdepolarizations, arising from the peak of the delayed afterdepolarization, suggesting that the possible mechanism of this induced ectopic beat was triggered activity.

The relation between the pacing cycle length and the amplitude of delayed afterdepolarizations is shown in Figure 3A. The amplitude of delayed afterdepolarizations at a pacing cycle length of 600 msec was 1.47±0.34

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<th>TABLE 1. Effects of Ouabain on Monophasic Action Potentials</th>
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Data are mean±SEM.

All data were obtained during sinus rhythm. The mean sinus cycle length was 617±35 msec in the control state and 619±37 msec after perfusion of ouabain (NS).

Amplitude, action potential amplitude; \( \text{APD}_{90} \) and \( \text{APD}_{90} \) action potential duration at 50% and 90% repolarization, respectively.
mV \((n=9)\). The amplitude increased progressively as pacing cycle length shortened and reached maximum at a pacing cycle length of 450 msec \((3.50\pm0.61 \text{ mV})\). When the pacing cycle length was further decreased, the amplitude decreased progressively. The amplitude at a cycle length of 200 msec was 0.73\pm0.19 mV.

The relation between the pacing cycle length and the coupling interval of delayed afterdepolarizations is shown in Figure 3B. The coupling interval of delayed afterdepolarizations at a cycle length of 600 msec was 628\pm29 msec, and it shortened progressively as the pacing cycle length was decreased. The coupling interval at a cycle length of 200 msec was 283\pm4 msec.

Response of Ouabain-Induced Ventricular Tachycardia to Overdrive Pacing

Sustained monomorphic VT was induced by ouabain in all 15 dogs. The mean concentration of ouabain

**FIGURE 2.** Tracings of induced delayed afterdepolarizations (panel A) and ectopic beat (panel B). Note the induced ectopic beat had the same coupling interval as the coupling interval of delayed afterdepolarizations. VP, ventricular pacing; CL, cycle length; ECG, electrocardiogram; MAP, monophasic action potential.

**FIGURE 3.** Panel A: Plot of pacing cycle length and amplitudes of delayed afterdepolarizations. Amplitude of delayed afterdepolarizations was maximum at a pacing cycle length of 450 msec \((3.50\pm0.61 \text{ mV})\). Panel B: Plot of pacing cycle length and coupling intervals of delayed afterdepolarizations. Coupling interval of delayed afterdepolarizations shortened as the pacing cycle length was reduced. DAD, delayed afterdepolarizations.
required to induce VT was 20.9±2.6 μg/kg (range, 3.9–30.0 μg/kg). Nine of 15 (60%) VTs had a constant cycle length (mean, 369±12 msec; range, 300–410 msec), whereas six (40%) had variations in the VT cycle length. The responses to rapid ventricular pacing were then studied in the nine dogs that demonstrated VTs with a constant cycle length. The morphology of QRS complexes during spontaneous VT and during pacing from the septal electrode catheter were identical in surface electrocardiographic leads I, II, III, aVR, aVL, aVF, and V₃, suggesting that the VT originated from the site of ouabain infusion. Figure 4 shows a representative example of the response of ouabain-induced sustained monomorphic VT to rapid ventricular pacing. When pacing was terminated, the original VT was reinitiated immediately (Figure 4A). The first postpacing impulse had a morphology identical to that of the original VT, in contrast to previous observations in which triggered arrhythmias were induced by systemic digitalis intoxication.¹⁹,²⁰ In those studies, the first postpacing impulse displayed morphology similar to those of paced QRS complexes. The recovery interval of the first postpacing impulse (500 msec) was longer than the original VT cycle length (420 msec) (Figure 4B). The coupling interval of the second postpacing impulse (380 msec) was shorter than the recovery interval of the first postpacing impulse, and the coupling interval of the successive postpacing impulses increased gradually and returned to the original VT cycle length (Figure 4B).

Figure 5 shows the coupling interval of the first postpacing impulse (expressed as the percentage of the cycle length of the original VT) as a function of pacing cycle length when pacing was performed at the RV outflow tract. At relatively long pacing cycle lengths, the coupling interval of the first postpacing impulse was longer than the cycle length of the original VT cycle (overdrive suppression). The coupling interval shortened progressively as the pacing cycle length was reduced. At pacing cycle lengths less than 65% of the cycle length of the original VT, the coupling interval of the first postpacing impulse was shorter than the cycle length of the original VT (overdrive acceleration).

Figure 6 shows the average of the coupling interval of 10 successive postpacing impulses at a pacing cycle length 65% to 75% of the original VT cycle length. The coupling interval of the second postpacing impulse was shorter than the recovery interval of the first postpacing impulse. The coupling interval of the successive postpacing impulses after the second impulse gradually increased and returned to the original VT cycle length a mean of 7±1 impulses after cessation of pacing.

These responses to rapid ventricular pacing were observed at all pacing sites tested. The coupling interval of the first postpacing impulse, however, was shorter when the pacing was performed closer to the ouabain infusion site (focus of VT). Figure 7 compares responses to ventricular pacing at a cycle length of 250 msec when pacing was performed at the LV septum (near pacing site) and the RV outflow tract (distant pacing site). The recovery interval of the first postpacing beat was 400 msec when pacing was performed at the LV septum, whereas the coupling interval was 460 msec when pacing was performed at the distant site (RV outflow tract).
VT. Two types of responses to rapid ventricular pacing were observed when pacing cycle length was slightly longer than the VT cycle length: 1) the QRS complexes were those of the original VT throughout pacing (i.e., VT was not modulated by rapid ventricular pacing), and 2) the QRS complexes were initially the same as the paced beat followed by progressive fusion of paced beats with the original VT and finally displayed the same morphology as the QRS complexes of the original VT (see Figure 8C). Two types of responses were also observed when pacing cycle length was slightly shorter than the VT cycle length: 1) the QRS complexes were those of paced beats throughout pacing, and 2) the QRS complexes were initially those of the original VT followed by progressive fusion of the VT impulses with paced beats and finally displayed the same morphology as the completely paced beat (see Figure 8E). Constant fusion was observed in a rare occasion when pacing cycle length was the same as the VT cycle length as shown in Figure 8D. This happened only in two dogs and was not always reproducibly observed even when the heart was repeatedly paced at the same cycle length. A slight fluctuation of the cycle length of VT made it impossible for constant fusion to occur.

**Effect of Verapamil**

After completion of the stimulation protocol, effects of perfusion of verapamil through the septal electrode catheter was tested in four dogs. Verapamil was perfused approximately 30–40 minutes after sustained VT developed. Perfusion of 0.015–0.034 mg/kg verapamil completely eliminated VT or PVCs in all four dogs. The suppression of VT was not due to a simple washout effect with Tyrode’s solution, because drug-free Tyrode’s solution was continuously perfused before verapamil was perfused. Before elimination of PVCs, bigeminy was sometimes observed. After the elimination of VT or PVCs, rapid ventricular stimula-

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**Figure 5.** Plot of normalized recovery intervals and normalized pacing cycle lengths. Recovery interval had a direct relation to the pacing cycle length. Slight overdrive suppression was observed at pacing cycle lengths of 0.75–0.95 of the original tachycardia cycle length. Overdrive acceleration was observed at pacing cycle lengths of 0.45–0.65 of the original tachycardia cycle length. RCL, recovery cycle length; BCL, basic cycle length; PCL, pacing cycle length.

**Fusion During Rapid Ventricular Pacing**

The demonstration of constant fusion during rapid pacing at a constant rate, except for the last captured beat and progressive fusion as pacing rate is increased, is the major criterion for transient entrainment of reentrant tachycardias. We, therefore, repeatedly performed rapid ventricular pacing at cycle lengths close to those of the VTs to determine whether criteria for transient entrainment were met by the focal triggered fusion.
tion no longer induced delayed afterdepolarizations or triggered ventricular beats (Figure 9).

Discussion

In this study, we designed a new model to study triggered activity and related arrhythmias in vivo. The unique feature of the model is the ability to elicit delayed afterdepolarizations and triggered activity in a controlled, limited, and specific area of the heart. The resultant arrhythmia, thus, resulted from focal triggered activity. With this model, the effects of overdrive pacing on focal triggered arrhythmias could be studied without influences of other potential foci of triggered activity. Of importance, the characteristics of responses to overdrive pacing of focal triggered arrhythmias were not only different from those of reentrant tachycardia, but also different in some ways from the triggered arrhythmias when the entire heart was potentially susceptible to triggered arrhythmias.

The responses of triggered arrhythmias to pacing when the entire heart is susceptible to triggered activity (i.e., global intervention) has been extensively studied.19–21 Only limited information, however, is available on the responses to pacing of triggered arrhythmias resulting from small areas of susceptible tissues. Malfatto et al21 studied triggered arrhythmias caused by anterior wall myocardial infarction, but they did not report on the morphology of the QRS complexes during pacing or after cessation of pacing. Because experimental data suggest focal triggered activity plays a role in the genesis of clinical arrhythmias,15,22,23 we developed this in vivo model of focal triggered arrhythmias. Several findings in the present study support our assumption that induced sustained VT originated from the site of ouabain infusion and that triggered activity arising from delayed afterdepolarizations may be an underlying mechanism of induced VT. First, the dose of ouabain required to induce sustained monomorphic VT was 20.9±10.0 μg/kg (range, 3.9–30.0 μg/kg), which is lower than the doses previously reported to induce sustained VT by intravenous infusion of ouabain. Iesaka et al31 reported that 93±16 μg/kg ouabain was required to induce sustained VT in normal dogs, and Malfatto et al21 reported that two of eight dogs tested developed sustained VT on infusion of 30–40 μg/kg ouabain and four on infusion of 60–80 μg/kg ouabain; two did not develop sustained VT. Thus, the doses we used were much lower than the doses required to develop systemic ouabain intoxication. Second, before development of sustained VT, MAPS recorded from the posterior wall, a site remote from the ouabain infusion site, were not modified. Delayed afterdepolarizations were recorded only from the septum, the site of ouabain infusion. Third, QRS complexes generated by pacing at the site of ouabain infusion had morphologies identical to those of the sustained VTs. Fourth, local perfusion of verapamil onto the site of ouabain infusion completely eliminated VT or PVCs. These observations indicate that the induced VT originated from the site of ouabain infusion. Finally, our findings suggest that the possible mechanism of the VT was triggered activity because delayed afterdepolarizations developed at the site of ouabain infusion, the ectopic beats occurred at the same coupling intervals as those of delayed afterdepolarizations, and perfusion of verapamil onto the focus suppressed the induced VT. However, there are limitations of the study, including the lack of systemic ouabain concentrations and only one reference MAP recording site distant from the site of ouabain perfusion. Thus, it is unclear to what extent the adjacent area of the site of ouabain infusion became electrically abnormal. Furthermore, the local concentration of verapamil was not determined and may be within a toxic range.

Delayed afterdepolarizations during rapid ventricular pacing were not recorded in four dogs after 10 μg/kg ouabain. The absence of delayed afterdepolarizations in these four dogs may be due to the technical difficulties of recording of delayed afterdepolarizations in dogs, as observed by Levine et al.29 Although we cannot exclude the possibility that induced VTs in these dogs were due to mechanisms other than triggered activity, they showed the same responses to overdrive pacing as did the VTs in dogs with delayed afterdepolarizations.

FIGURE 7. Tracings of coupling interval of postpacing impulses after pacing at the left ventricular side of the intraventricular septum (panel A) and the right ventricular outflow tract (panel B). After pacing at the septum, the recovery interval of the first postpacing impulse was 400 msec, which was shorter than the recovery interval of the first postpacing impulse (460 msec) after pacing at the right ventricular outflow tract (distant pacing site). LV, left ventricular; VP, ventricular pacing; CL, cycle length; RV, right ventricular.
The characteristic responses of focal triggered arrhythmias to overdrive pacing included four elements. First, on cessation of pacing, the original VT was reinitiated immediately with the same morphology as the original VT, as seen after transient entrainment of reentrant arrhythmias. Second, the recovery interval of the first postpacing impulse had a direct relation to the pacing cycle length. The recovery interval showed slight overdrive suppression at a relatively long pacing cycle length, and overdrive acceleration at a short pacing cycle length. Third, the recovery interval of the first postpacing impulse is dependent on the site of stimulation. The recovery interval is shorter when the pacing site is closer to the focus of origin. Fourth, the coupling interval of the second postpacing impulse is shorter than the recovery interval of the first postpacing impulse. The coupling intervals of the successive postpacing impulses increase gradually.

The most distinct difference in the responses to overdrive pacing between our study and the studies by Gorgels et al. was the morphology of the first postpacing impulse. In the latter studies, in which the heart was globally susceptible, the first postpacing impulse had the same morphology as the original VT when pacing was performed close to the origin of VT, whereas it had the same morphology as the paced impulse when pacing was performed at a distant site. Of the multiple potential ventricular foci of triggered activity, a dominant focus gives rise to the spontaneous VT, but other ventricular foci can be triggered by pacing and can be discharged earlier than the dominant focus. In contrast, our model had only one focus at the site of ouabain infusion. Thus, wherever the pacing site was, the first postpacing beat always had a morphology identical to that of the original VT.

In our study, the coupling interval of the second postpacing impulse was shorter than the first postpacing interval, and the coupling interval after the second postpacing impulse increased gradually. This may be explained by the fact that the coupling interval of the first postpacing impulse included the conduction time from the stimulation site to the focus and the time for reset of the discharge interval of triggered activity at the focus, whereas the coupling interval after the second postpacing impulse is composed of only the time for reset of the discharge interval of the focus. In the model used by Malfatto et al. characterized by multiple foci, the focus that reached threshold fired randomly, and thus, the coupling interval and morphologies of the successive postpacing impulses were variable. Our findings that the first postpacing interval was shorter when the pacing site was closer and that it was longer when the pacing site was at a distance can also be explained by the recovery interval of the first postpacing interval that included the conduction time from the stimulation site to the focus.

Constant fusion beats during pacing at a constant rate faster than the rate of the tachycardia, except for the last captured impulse, which is entrained but not fused, is an important criterion for transient entrainment. In our study, when pacing was performed at a cycle length close to the VT cycle length, the QRS complexes during pacing displayed a variable degree of fusion between the paced impulse and the VT impulse. Constant fusion only occurred at a pacing cycle length identical to that of the spontaneous VT, and thus, by definition, the VT could not possibly have been entrained.

**Figure 8.** Tracings of various fusion beats during pacing at cycle lengths close to the tachycardia cycle length. Original ventricular tachycardia with a cycle length of 330 msec (panel A), and paced rhythm at a pacing cycle length of 320 msec (panel B). During pacing at a cycle length slightly longer than the ventricular tachycardia cycle length (332 msec), QRS complexes were initially those of the paced impulses followed by increased fusion with the original ventricular tachycardia, and they finally showed the same morphology as the original ventricular tachycardia (panel C). During pacing at the same cycle length (330 msec) as the tachycardia cycle length, a few instances of constant fusion were observed throughout the pacing (panel D). During pacing at a cycle length slightly shorter than the tachycardia cycle length (328 msec), QRS complexes were initially the same as the ventricular tachycardia followed by gradually increasing fusion with the paced impulses and finally showed the same morphology as the paced impulses (panel E). VT, ventricular tachycardia; CL, cycle length; VP, ventricular pacing.
Finally, of note, several lines of experimental evidence suggest that triggered activity induced by different methods respond to pacing in different ways.11-16,21,32,33 Thus, it is not possible to obtain unequivocal evidence of the underlying cause of an arrhythmia only by analysis of coupling intervals and responses to pacing.

References
27. Autenrieth G, Surawicz B, Kuo CS: Sequence of repolarization on the ventricular surface in the dog. Am Heart J 1975;89:463–469

KEY WORDS • triggered activity • delayed afterdepolarization • monophasic action potential • ouabain
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Circulation. 1990;82:549-559
doi: 10.1161/01.CIR.82.2.549

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

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