Effect of Propranolol, Procainamide, and Lidocaine on Ventricular Automaticity and Reentry in Experimental Myocardial Infarction

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SUMMARY
The importance of two arrhythmogenic mechanisms, ventricular reentry and automaticity, was assessed after coronary ligation in 35 cats. Automaticity was estimated by the frequency of ventricular escape beats after intravenous acetylcholine, and reentry was estimated by the number of repetitive beats induced by premature ventricular stimuli. Increased automaticity only was present after coronary ligation in two studies; increased reentry only was noted in 24; and both increased automaticity and reentry were seen in nine studies. Incremental doses of lidocaine (2-4 mg/kg), propranolol (0.1-0.3 mg/kg), or procainamide (5-15 mg/kg) consistently returned automaticity to normal. Procainamide abolished repetitive beats in 12 of 13 studies, propranolol did so in eight of 11, but lidocaine did so in only six of 17. Repetitive beats actually increased in six studies after lidocaine, at a time when lidocaine blood levels were in the lower therapeutic range. A persistent arrhythmia appeared after coronary ligation in 12 studies; in 10 the disappearance or persistence of the arrhythmia after drug administration matched the disappearance or persistence of repetitive beats. We conclude that both reentry and increased ventricular automaticity appear during myocardial infarction but that reentry seems of greater importance in the genesis of arrhythmias. These drugs are more reliable in normalizing automaticity than in abolishing reentry; the failure of a drug may thus be related to its failure to abolish reentry. Moreover, lidocaine may accentuate ventricular reentry, especially at the lower blood levels.

Additional Indexing Words:
Antiarrhythmic drug Ventricular extrasystoles Acetylcholine Arrhythmias
Parasympathetic stimulation Ventricular tachycardia

The unpredictable effect of antiarrhythmic drugs is well known and is probably related to the varying mechanisms of arrhythmias as well as to the diverse electrophysiologic effects of the antiarrhythmic agents. It is generally believed that two electrophysiologic abnormalities account for many arrhythmias: (1) disturbances of conduction, leading to reentrant circuits; and (2) disturbances of impulse formation, due to increased automaticity.1-3

Recent electrophysiologic studies of antiarrhythmic drugs have elucidated several mechanisms by which these drugs might affect rhythm disturbances.1 Although all of the commonly used antiarrhythmic agents reduce the rate of diastolic depolarization of Purkinje cells, they differ in other respects from one...
another: the rate of rise of phase 0, conduction velocity, action-potential duration, and effective refractory period are variably affected by these agents, and thus their effect on the reentrant phenomenon remains speculative.

Most of the evidence regarding the antiarrhythmic effect of drugs is based on studies of isolated fibers using microelectrode techniques, and information about the relative effectiveness of these drugs in the intact animal is sparse.4-6 Since no previous studies have determined whether antiarrhythmic drugs act on ventricular tachycardias or extrasystoles by reducing automaticity or by affecting reentry, this investigation was undertaken. The study was designed to evaluate ventricular automaticity and reentry during myocardial infarction in the intact cat and to observe the effect of three antiarrhythmic agents—lidocaine, propranolol, and procainamide—on these two mechanisms.

Method

Myocardial infarction was produced in cats by ligating the left anterior descending coronary artery. Repetitive beats, evoked by premature ventricular stimuli, were used as a measure of reentry. The number of ventricular escape beats occurring during parasympathetic stimulation was used to assess ventricular (Purkinje) automaticity. Automaticity, reentry, and rhythm were studied before and after coronary ligation and again after giving an antiarrhythmic agent.

The cats were anesthetized with intravenous pentobarbital, 30 mg/kg, and the chest was opened by left thoracotomy. Arterial pH and blood gases were monitored, with corrections made to prevent severe respiratory or metabolic imbalance.

Measure of Automaticity and Reentry

Acetylcholine, 1-5 mg, was rapidly injected into the femoral vein to produce A-V block. The number of ventricular beats occurring in the 10 sec after the onset of acetylcholine effect was the measure of Purkinje automaticity used. Acetylcholine was substituted for the more traditional vagal stimulation as a means of inducing parasympathetic response because it was found that unilateral or bilateral vagal stimulation in cats sometimes merely slows the sinus rate without producing atrial arrest or complete A-V block. Although acetylcholine may slow phase 4 depolarization of Purkinje cells,7 a comparison of the two techniques, vagal stimulation and acetylcholine administration, indicated that they yield similar estimates of ventricular automaticity (unpublished observation). Using both dogs and cats, the effects of the two were compared after digitalis in four preparations and after coronary ligation in two others. During control determinations 3 ± 0.8 ventricular beats occurred in the first 10 sec of vagal stimulation and 3 ± 0.7 beats occurred after acetylcholine. After digitalis (before toxic arrhythmias had appeared), and after coronary ligation, the mean increase in ventricular beats during vagal stimulation was 17 ± 2.1; after acetylcholine it was 11 = 2.9. Thus, although the increase in the number of ventricular beats was slightly less with acetylcholine, an increase in ventricular automaticity was evident by either method. There was no correlation between dose of acetylcholine and changes in ventricular automaticity.

The number of repetitive beats evoked by one or two premature ventricular electrical stimuli was used as a measure of reentry. A bipolar electrode, composed of gold-tipped stainless-steel needles fixed in plastic 2 mm apart, was placed in the left ventricular myocardium outside the expected area of infarction. Driving and premature pulses were delivered through the same electrode by S1 and S8. Grass pulse generators connected in parallel to Grass isolation units and constant-current units. A pulse of 2- or 10-msec duration twice diastolic threshold drove the heart (S0) at a rate of 2.5-3.5 Hz; both duration and rate were kept constant throughout an experiment. Single or pairs of premature stimuli, S1 and S2, were given to test for repetitive beats. S1 and S2 were delivered in combinations of 2x, 5x, and 10x threshold, with threshold defined as the minimum amperage necessary to drive the heart at a given rate. S1 was positioned 5 msec outside the S0 refractory period by observing the sweep on an oscilloscope. The refractory period often changed during an experiment, but the timing of S1 with respect to S0 refractory period was kept constant. S2 was positioned 5-20 msec outside the S1 refractory period. Each test for repetitive beats was repeated at least three times and only when repetitive beats appeared in at least two of the three tests were they accepted as being present. An ECG was recorded from limb lead II at paper speeds of 25 or 100 mm/sec.

Preliminary studies in our laboratory convinced us that it was possible to distinguish between ventricular beats which originated from an ectopic focus (due to increased automaticity) and beats due to reentry. During conditions of digitalis toxicity, when ventricular automaticity is augmented (unpublished observation), there was a pause longer than the driving interval between a prematurely stimulated ventricular response and
the ventricular beat which sometimes followed. These beats often appeared after a series of paced beats, when the pacing stimulus was merely turned off and no premature stimulus was given, and they showed no consistent temporal relationship to the premature stimuli. Repetitive reentrant beats were seen during preliminary studies in animals in which there was no evidence of increased automaticity after coronary ligation. A difference of even 5–10 msec in the prematurity of the stimulus was often critical in the evocation of a repetitive ventricular response. Such beats were reproducibly coupled to the premature ventricular stimuli and appeared early in diastole on or near the wave of the preceding beat. They did not occur if the pacing stimulus was simply turned off in the absence of a premature stimulus.

**Coronary Ligation**

Myocardial infarction was produced by ligating the left anterior descending coronary artery approximately 1.5 cm from its origin. If ventricular fibrillation developed, at least 10 min was allowed for recovery. Recurrent ventricular fibrillation, unless reproduced by stimuli of the same strength, duration, and position, was reason to terminate a study.

**Antiarrhythmic Drugs**

Although a drug was given anywhere from 45 min to 3 hours after coronary ligation, comparisons of ventricular automaticity and reentry were based on data obtained during the 15-min interval just before the drug was given and during the period 4–15 min afterward. Thus, the probability of spontaneous variation in these parameters was diminished.

Procaïnamide (5 mg/kg), lidocaine (2 mg/kg), and propranolol (0.1 mg/kg) were given as intravenous injections over 1–2 min and no more than one drug was given in each experiment. The dose was repeated one or two times if either the arrhythmias or repetitive beats persisted or if automaticity remained abnormally high; evidence of drug toxicity (severe bradycardia, cardiac arrest) constituted reason for terminating the study.

**Number of Studies**

Although myocardial infarction was produced in 52 cats, data on only 35 of these are presented (table 1). Thirteen of the remaining 17 could not be studied because of refractory repetitive ventricular fibrillation, and the remaining four were terminated because neither increased automaticity nor evidence of reentry was present.

**Results**

**Purkinje (Ventricular) Automaticity**

Ventricular automaticity, low at baseline, increased in 11 of 35 studies after coronary ligation; repetitive beats were also present in all but two of these. Propranolol, procaïnamide, or lidocaine returned automaticity to control values (fig. 1) in all but one instance. In the 24 studies in which automaticity did not increase after coronary ligation, it remained low throughout the study.

**Repetitive Beats**

Repetitive beats were present after coronary ligation in 33 of the 35 animals. Procaïnamide abolished repetitive beats in 12 of 13 studies and propranolol did so in eight of 11 (figs. 2, 3). Lidocaine abolished or decreased repetitive beats for more than 15 min in only six of

**Table 1**

<table>
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<th>VA only</th>
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<td>—</td>
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<td>9</td>
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<td>6</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>12</td>
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</table>

Abbreviations: RB = repetitive beats; VA = ventricular automaticity; VF = ventricular fibrillation.

*In four studies RB consistently progressed to ventricular VF.
†The arrhythmia appeared after coronary ligation but disappeared before drug could be given.
‡The arrhythmia persisted long enough so that the effect of a drug on the arrhythmia could be assessed.

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PROPRANOLOL, PROCAINAMIDE, & LIDOCAINE IN MI

A. Post Coronary Ligation

Acetylcholine Effect

![Graph showing Acetylcholine Effect]

B. Post Lidocaine

Acetylcholine Effect

![Graph showing Acetylcholine Effect]

Figure 1

Record during a study in which lidocaine was given. $S_0$ = driving stimulus. $S_1$ = first premature stimulus. $S_2$ = second premature stimulus. $\uparrow$ = repetitive beat. (A) Left side of strip shows a late repetitive response following $S_2$. Right side of strip shows the first 4 sec of response to acetylcholine injection. Automaticity is increased. Repetitive ventricular response may be due to either reentry or increased automaticity. (B) Left side of strip: a repetitive beat with shorter coupling interval follows $S_0$ response. Right side of strip, showing acetylcholine effect, indicates that ventricular automaticity had been returned to control values. (An arrhythmia, present before lidocaine, was still present.)

17 studies. Repetitive beats, ventricular fibrillation, or both remained through the entire 15-min test period after lidocaine was given in five experiments. In three of the five the number of repetitive beats was actually increased after lidocaine (fig. 4), while, in one other, test stimuli consistently produced ventricular fibrillation. In six other studies repetitive beats, although abolished initially, reappeared from 8 to 14 min after the drug had been given; in two of the six the number of repetitive beats was increased. Automaticity remained low at this time. Thus, lidocaine failed to eliminate repetitive beats in 11 of the 17 experiments, and in six of the 11 the number of repetitive beats increased or ventricular fibrillation supervened. Because of these unexpected results, lidocaine blood levels were measured at 3-min intervals in four animals after giving 2 mg/kg over 1½ min. Mean blood levels at 3 min were 3.9 $\mu$g/ml (range 2.8–4.9 $\mu$g/ml), falling to 1.9 $\mu$g/ml (1.5–2.3 $\mu$g/ml) at 6 min, 1.6 $\mu$g/ml (1.6–1.7 $\mu$g/ml) at 9 min and to 1.1 $\mu$g/ml (0.9–1.2 $\mu$g/ml) at 15 min. Thus, the tests were carried out when lidocaine blood levels were below toxic values, within the range considered to be therapeutic in humans (1.5 $\mu$g/ml), but often toward the lower limits. In all but one study, incremental doses of
lidocaine were administered 15–30 min apart until either reentry was extinguished or a marked bradycardia appeared.

In four experiments the coupling interval of the repetitive beats (interval from premature beat to repetitive beat) was shorter after giving lidocaine than before (fig. 4). In contrast, the coupling interval was increased...
PROPRANOLOL, PROCAINAMIDE, & LIDOCAINE IN MI

A. Post Coronary Ligation

B. Post Lidocaine

Figure 4

Record during a study in which lidocaine was given. (A) A single repetitive beat follows S2. (B) Two repetitive beats with shorter coupling interval follow S2. (Ventricular automaticity, which had increased after coronary ligation, had been returned to control values. A transient arrhythmia was present after coronary ligation.)

Arrhythmias

An arrhythmia appeared after coronary ligation in all 11 studies in which ventricular automaticity was increased (table 1). In contrast, an arrhythmia occurred in only 10 of the 24 experiments in which ventricular automaticity remained low.

The arrhythmia was persistent enough to permit comparison of the effect of a drug on an arrhythmia with its effect on repetitive beats and automaticity in 12 studies. In all 12, repetitive beats were present, and in seven ventricular automaticity was also increased. In 10 studies the disappearance or persistence of the arrhythmia after the drug had been given matched the disappearance of persistence of repetitive beats. There was no comparable relationship between ventricular automaticity and the arrhythmia. In six of seven studies in which automaticity had been increased after coronary ligation, the arrhythmia remained after automaticity had returned to control values, whereas the repetitive beats persisted in five of six. An arrhythmia was present in only two studies after repetitive beats were eliminated. In one, automaticity remained slightly above control values, and in the other the premature ventricular contractions became less frequent as ventricular automaticity and repetitive beats were returned to control values.

Discussion

Critique of Method

Evidence is abundant that critically timed premature stimuli can create the conditions necessary for reentry.8–12 The groups of Mendez, Anderson, and Hoffman, using Purkinje muscle preparations, have demonstrated that premature impulses may be conducted slowly in some parts of the system and blocked entirely in others and that this block may be unidirectional.8–10 Reentry has been demonstrated in the intact heart following premature stimuli.11, 12 Han12 demonstrated reentry in dogs after coronary occlusion by means of a premature impulse which was initiated by early ventricular stimuli and slowly conducted through an infarcted area, emerging to reexcite the entire heart and giving rise to one or more closely coupled repetitive beats.

Other mechanisms (transient or persistent increments in automaticity) which might account for these repetitive beats were considered. Prolonged application of direct current may alter phase 4 depolarization and, therefore, the possibility exists that the test stimuli caused ectopic foci to develop transiently with
the resulting repetitive response due to spontaneous firing of the artificially induced focus. It is also possible that premature stimuli decrease the threshold, permitting latent pacemaker cells to fire spontaneously. Arguments against these possibilities are: (1) If repetitive beats originated from such an artificially induced focus, the timing of the premature stimuli should not have been critical. (2) The two phenomena, repetitive beats and increased automaticity, often appeared or disappeared independently of one another. (3) If closely coupled repetitive beats originated from ectopic foci, one would expect to see them consistently in conditions of digitalis toxicity where Purkinje automaticity is increased. Our observations that ventricular beats following premature stimuli in digitalis toxicity were characterized by a pause coincide with those of Hagemeijer and Lown,13 this group also noting that such late beats appeared to be manifestations of increased automaticity rather than reentry. Thus, although not proved unequivocally, the most plausible explanation for closely coupled repetitive beats in response to premature electrical stimuli is that they are due to reentry.

The relatively wide spacing of ventricular beats which occur during parasympathetic stimulation (fig. 1) is evidence that these beats are due to automaticity rather than to reentry, since reentrant circuits should not take such prolonged periods. Although Cranefield and Hoffman have shown that low effective conduction velocities may result from the summation of two previously blocked impulses,14 it seems unlikely that this mechanism occurs with such regularity as to account for the ventricular beats seen during acetylcholine effect. Moreover, in digitalis toxicity, where phase 4 depolarization is known to be increased, a similar increase in the number of widely spaced ventricular escape beats occurs during parasympathetic stimulation. Although cardiac arrest, whether produced by vagal stimulation or acetylcholine, may evoke a sympathetic response which in turn can increase ventricular automaticity, this extraneous effect is expected to play an equal role before and after coronary ligation and after administration of a drug. A possible sympathetic effect on automaticity, therefore, does not invalidate the method, a point further supported by the observation that ventricular automaticity was low before coronary ligation and after drug administration.

**Effect of Drugs on Automaticity and Reentry**

Each of the drugs used in this study is known to decrease the slope of phase 4 depolarization and would thus be expected to abolish arrhythmias due to increased Purkinje automaticity.1 Although propranolol, procainamide, and lidocaine were found to be equally effective in reducing automaticity to control values, the fact that an arrhythmia sometimes persisted suggests that other mechanisms were responsible for the continued presence of the arrhythmia.

The effect of antiarrhythmic agents on the reentrant phenomenon is much less predictable since these drugs are known to have multiple electrophysiologic actions.1 Thus, the observation that their effect on reentry was less consistent than their effect on increased ventricular automaticity was not unexpected. Perhaps the most interesting observation was that the two drugs which slow Purkinje-ventricular conduction, propranolol and procainamide, abolished the reentrant phenomenon in the majority of studies. The observation that in five instances an initial dose of these drugs widened the coupling interval of the repetitive beats and a subsequent dose resulted in their total extinction makes it possible to speculate on a mechanism which could account for their beneficial effect. The coupling interval may have increased because the impulse was conducted more slowly along the existing reentrant pathway. The additional dose might have changed unidirectional block to bidirectional blockade, thereby eliminating reentry entirely.15

The more frequent failure of lidocaine to abolish reentry was unexpected in view of its general success in controlling ventricular arrhythmias in clinical circumstances. Its inefficacy after myocardial infarction has also
been demonstrated by others recently.\textsuperscript{6,16} There is little likelihood that lidocaine failure in our investigations was due to toxic amounts of the drug, since virtually all tests were performed at a time when the lidocaine blood level was below that considered toxic in humans. Since blood levels dropped rapidly in the first minutes, it is more likely that our observations were made when they were relatively low, although still within the therapeutic range of the drug.\textsuperscript{1} The fact that in six studies repetitive beats or ventricular fibrillation were more frequent after lidocaine suggests that when blood levels are near the currently accepted lower therapeutic limit (1–2 $\mu$g/ml) the likelihood of reentry may actually increase.

One may speculate on the reasons for the intermittent failure of lidocaine. The finding that lidocaine, unlike the other two drugs, shortened the coupling interval for repetitive beats, suggests that this agent may increase conduction velocity,\textsuperscript{17} but sometimes not enough to interrupt reentrant circuits. The reappearance of repetitive beats after they had been abolished initially suggests that the degree of decrement and block might have been such that at the higher blood levels lidocaine was present in amounts sufficient to enhance conduction and to eliminate block, thereby preventing reentry, but as lidocaine blood levels fell the enhancement of conduction became insufficient and reentry reappeared. Lidocaine might even accentuate a reentrant arrhythmia if, by decreasing decremental conduction, an area of bidirectional blockade were converted to one of unidirectional conduction.

Genesis of Arrhythmia in Myocardial Infarction

Both increased automaticity and reentry appear after coronary ligation and thus both might contribute to the arrhythmias seen in this condition. Reentry seems to be the more influential, as it was present more often following coronary ligation and was better correlated with the presence or absence of an arrhythmia after a drug has been given. In several instances, although automaticity had been returned to control values, both repetitive beats and the arrhythmia persisted; once an arrhythmia had been abolished it was not possible to elicit repetitive beats.

Limitations of the Study

It should be emphasized that these studies were done in healthy animals; it is unlikely that previous infarctions were present. Antiarrhythmic drugs were given during the first 4 hours after coronary ligation and, therefore, earlier than treatment is usually begun in clinical circumstances. The experiments were performed in cats; if the geometry of reentrant cycles is important to their existence, myocardial mass would be a factor. Finally, bradyarrhythmias, important in the genesis of ventricular tachycardia and fibrillation in clinical situations, were obviated by using ventricular pacing.

Therefore, extrapolation of our observations to myocardial infarction in man is justified in only a limited sense. Although we hesitate to conclude that lidocaine is inferior to propranolol and procainamide in the therapy of arrhythmias in myocardial infarction, our findings suggest that in certain circumstances, perhaps at lower blood levels, perhaps when given soon after infarction occurs, lidocaine may be ineffective and even harmful. The principal value of the study rests with the observations that: (1) both increased ventricular automaticity and reentry appear during myocardial infarction; (2) although each may be instrumental in the genesis of arrhythmias in myocardial infarction, reentry seems of greater importance; and (3) since the drugs appear more reliable in normalizing automaticity than in abolishing reentry, the occasional failure of a drug may be related to its failure to abolish reentry.

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References

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