ABSTRACT
Lidocaine was administered as a rapid intravenous bolus injection followed by a constant-rate intravenous infusion to nine dogs with 2-hour-old myocardial infarctions. Bipolar electrograms were recorded from and effective refractory periods were determined in the infarcted and normal zones of the heart. Intervals (Q-EG) were measured from the onset of the QRS complex in a standard electrocardiogram limb lead to the major deflection of the recorded electrograms from the normal and infarcted zones. QRS duration and serum lidocaine concentration were also determined. At serum concentrations considered to be therapeutic, lidocaine prolonged the Q-EG intervals in the infarcted zones of the heart 17-26% at peak effect (P < 0.01), but it had no effect on the Q-EG intervals in the normal zone except for a slight (1.5%) prolongation shortly after the initial intravenous bolus injection. Lidocaine also had no effect on QRS duration. Similarly, lidocaine prolonged the effective refractory period of the infarcted zone 23% (P < 0.01) at peak effect but had no effect on the effective refractory period of the normal zone. Prior to lidocaine administration, the mean effective refractory period of the normal zone was 26 msec longer than that of the infarcted zone, but at peak drug effect the disparity in refractoriness was reduced to 1 msec. The present study thus shows that lidocaine has different effects in infarcted and normal zones of the heart. In delaying activation and prolonging the effective refractory period of the infarcted zone of the heart, lidocaine has local anesthetic actions which might explain its effectiveness in curtailing ventricular arrhythmias after acute myocardial infarction.

KEY WORDS atrial pacing conduction intervals infarcted zone Vmax bipolar electrograms

Lidocaine is used widely in acute myocardial infarction for both the prevention and the treatment of ventricular arrhythmias (1-6). Although its effectiveness in curtailing such arrhythmias is clear, the mechanism of its antiarrhythmic properties is still uncertain. Speculation on the mechanism of lidocaine's action in controlling ventricular arrhythmias after infarction is based largely on data from isolated cardiac tissues rather than from infarcted hearts (7, 8). Consideration of the effects of lidocaine on conduction and refractoriness has been an important part of these microelectrode studies, since alterations in these parameters are believed to be important in the genesis of reentrant arrhythmias (9, 10) and thus in their abolition.

In the microelectrode studies to date, concentrations of lidocaine considered to be therapeutic and not toxic have had little effect on or have enhanced the maximum rate of rise (Vmax) of the Purkinje fiber and the ventricular muscle action potential (7, 11, 12); Vmax correlates with the rate of conduction of an impulse (13). Lidocaine also causes a shortening of the action potential duration of both Purkinje fibers and ventricular muscle, but it results in significant shortening of the effective refractory period only in the case of Purkinje fibers (7, 11, 12). These actions of lidocaine differ from those of other local anesthetic antiarrhythmic agents which, in concentrations considered to be therapeutic, reduce Vmax and prolong the action potential duration and the effective...
Effects of Lidocaine in Infarction

The effects of myocardial infarction on the refractory period of both Purkinje fibers and ventricular muscle (10, 14). Because of these differences, lidocaine has been thought to exert its action in controlling ventricular arrhythmias in a different manner (8, 12).

However, there are limitations in extrapolating data obtained from microelectrode studies on isolated nondepressed tissue in vitro to in situ hearts with acute myocardial infarction (15, 16). Therefore, in the present study lidocaine was administered to dogs with acute myocardial infarction, and its effects on intracardiac conduction intervals and the effective refractory period in normal and infarcted zones of the heart were determined.

Methods

In nine adult mongrel dogs anesthetized with sodium pentobarbital (30 mg/kg, iv) and mechanically ventilated, a midsternal thoracotomy was performed and the heart exposed. The experimental preparation is illustrated in Figure 1. Acute myocardial infarctions were created by two-stage ligation of the left anterior descending coronary artery distal to the first or second diagonal branch according to the method of Harris (17). Silver electrodes embedded in acrylic plaques were sewn on the right atrial epicardium and the right ventricular epicardium at a site distant from the infarcted zone. An intramyocardial electrode (a 23-gauge needle with ten silver electrodes mounted 1 mm apart) was inserted in the left ventricle toward the periphery of the infarcted zone. The base of the needle was mounted on an acrylic plaque and sutured to the left ventricular epicardium to prevent motion of the needle.

Bipolar atrial pacing was performed at constant R–R intervals ranging from 330 to 400 msec between dogs. Bipolar electrograms were recorded between filter frequencies of 12 and 500 Hz from the normal zone in the right ventricle and from successive pairs of electrodes on the intramyocardial electrode in the infarcted zone (Fig. 1). A standard electrocardiogram (ECG) limb lead was recorded simultaneously between filter frequencies of 0.1 and 500 Hz. The intervals from the onset of the QRS complex to the major deflection of the bipolar electrograms recorded in the infarcted and normal zones were measured and labeled Q–EG intervals. In the infarcted zone, the Q–EG intervals were numbered Q–EG-1 (innermost) to Q–EG-5 (outermost). Prolongation of the Q–EG interval in either the infarcted or the normal zone was considered to represent a delay in ventricular or Purkinje fiber conduction, or both; since the sequence of ventricular activation was normal with atrial pacing of the heart, there was maximum participation of the Purkinje system in cardiac conduction. The effective refractory period was determined with programmed premature stimuli of two times diastolic threshold delivered after every tenth atrially paced beat into electrodes previously used for recording in the infarcted and normal zones.

Two hours after complete ligation of the left anterior descending coronary artery, Q–EG intervals and effective refractory periods were stable over a 30-minute control period. Commercially available lidocaine for cardiac use (Xylocaine, Astra) was then administered as a 2-mg/kg rapid intravenous bolus injection followed by a constant-rate intravenous infusion of 4.3 mg/kg hour for 2 hours. Q–EG intervals, effective refractory periods, and serum lidocaine concentrations were determined during the lidocaine infusion and for 2 hours after the infusion had been discontinued.

After these determinations had been made, the dog was killed, and the intramyocardial electrode was removed with a wedge of myocardium surrounding it. In one instance, two electrodes of the intramyocardial electrode were within the left ventricular cavity and not within the left ventricular myocardium; electrograms recorded from these two electrodes were not included in the data.

Serum lidocaine concentrations were determined by gas chromatography (18) performed by the Astra Corporation. Statistical evaluation of the percent changes in Q–EG intervals and effective refractory periods from control values were performed using Student's t-test; calculations were performed on a digital PDP-11 computer.

Results

The effects of myocardial infarction on the
timing of electrograms recorded in the infarcted zone, the wave form of the bipolar electrograms recorded in the infarcted zone, and the effective refractory period determined in the infarcted zone were similar to those found in previous studies of dogs with acute myocardial infarction (19, 20). Although there was great variability in these effects, in general, following coronary artery ligation Q-EG intervals were prolonged, the sequence of activation was highly variable, the recorded electrograms were prolonged, and the effective refractory period in the infarcted zone was shortened. For each dog these changes all became stable within 1.5 hours following infarction, and after an interval of another 30 minutes the lidocaine infusion was begun.

![Diagram](http://circres.ahajournals.org/content/36/1/86/F2.expansion.png)

**Figure 2**

Effect of lidocaine on Q-EG intervals and effective refractory periods (ERP) in the infarcted and normal zones of the heart and on QRS duration. The broken lines indicate determinations made in the infarcted zone and the dotted lines indicate those made in the normal zone. The top curve shows the serum lidocaine concentration in µg/ml ± se during and after the lidocaine infusion; the lidocaine infusion was discontinued at 120 minutes. The second curve (Q-EG-5) shows the changes in the Q-EG-5 interval, determined using a representative pair of electrodes on the intramyocardial electrode in the infarcted zone, during and after the lidocaine infusion, the third curve (Q-EG(NL)) shows the changes in the Q-EG interval in the normal zone, the fourth curve (QRS) shows the changes in QRS duration, the fifth curve (ERP(INF)) shows the changes in the effective refractory period in the infarcted zone, and the bottom curve (ERP(NL)) shows the changes in the effective refractory period in the normal zone. Each point on these curves represents the mean percent change ± se from control values determined before lidocaine was administered. The asterisks indicate P < 0.01 and the double daggers indicate P < 0.05. See text for further discussion.

*Circulation Research, Vol. 36, January 1975*
### TABLE 1
Lidocaine Concentrations, Q-EG Intervals, QRS Durations, and Effective Refractory Periods

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Lidocaine concentration (µg/ml)</th>
<th>Q-EG intervals in infarcted zone (%) change</th>
<th>Q-EG interval in normal zone (µg/ml) (% change)</th>
<th>QRS duration (µg/ml) (% change)</th>
<th>Effective refractory period (infarcted zone) (%) change</th>
<th>Effective refractory period (normal zone) (%) change</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5.3 ± 0.7</td>
<td>13 ± 4*</td>
<td>14 ± 4†</td>
<td>10 ± 2*</td>
<td>9 ± 1.5*</td>
<td>1.5 ± 0.5†</td>
</tr>
<tr>
<td>10</td>
<td>4.2 ± 0.8</td>
<td>15 ± 4*</td>
<td>15 ± 3*</td>
<td>17 ± 1.5*</td>
<td>14 ± 3*</td>
<td>10 ± 2*</td>
</tr>
<tr>
<td>15</td>
<td>3.0 ± 0.4</td>
<td>13 ± 4*</td>
<td>16 ± 2*</td>
<td>16 ± 1.5*</td>
<td>15 ± 2*</td>
<td>11 ± 3*</td>
</tr>
<tr>
<td>30</td>
<td>2.35 ± 0.2</td>
<td>9 ± 3*</td>
<td>13 ± 4†</td>
<td>9 ± 2.5*</td>
<td>14 ± 3*</td>
<td>8 ± 4†</td>
</tr>
<tr>
<td>45</td>
<td>2.5 ± 0.3</td>
<td>14 ± 3*</td>
<td>18 ± 3.5†</td>
<td>16 ± 2*</td>
<td>18 ± 2*</td>
<td>12 ± 3*</td>
</tr>
<tr>
<td>60</td>
<td>3.1 ± 0.3</td>
<td>17 ± 3*</td>
<td>20 ± 3*</td>
<td>18 ± 2*</td>
<td>20 ± 2.5*</td>
<td>17 ± 2*</td>
</tr>
<tr>
<td>75</td>
<td>3.3 ± 0.4</td>
<td>16 ± 2*</td>
<td>21 ± 5†</td>
<td>20 ± 4*</td>
<td>23 ± 2.5*</td>
<td>18 ± 4†</td>
</tr>
<tr>
<td>90</td>
<td>3.1 ± 0.4</td>
<td>21 ± 5*</td>
<td>26 ± 4*</td>
<td>20 ± 1.5*</td>
<td>20 ± 1.5*</td>
<td>18 ± 3*</td>
</tr>
<tr>
<td>120</td>
<td>3.3 ± 0.3</td>
<td>19 ± 2.5†</td>
<td>22 ± 2*</td>
<td>20 ± 1.5*</td>
<td>19 ± 2*</td>
<td>17 ± 1*</td>
</tr>
<tr>
<td>After Termination of Lidocaine Infusion</td>
<td>15</td>
<td>1.9 ± 0.3</td>
<td>11 ± 4*</td>
<td>16 ± 3*</td>
<td>12 ± 4†</td>
<td>13 ± 4†</td>
</tr>
<tr>
<td>30</td>
<td>1.3 ± 0.2</td>
<td>4 ± 2</td>
<td>11 ± 3†</td>
<td>10 ± 3</td>
<td>9 ± 4</td>
<td>5 ± 3</td>
</tr>
<tr>
<td>45</td>
<td>1.1 ± 0.3</td>
<td>3 ± 2</td>
<td>6 ± 3</td>
<td>6 ± 3</td>
<td>9 ± 3</td>
<td>4 ± 2</td>
</tr>
<tr>
<td>60</td>
<td>1.0 ± 0.3</td>
<td>3 ± 3</td>
<td>7 ± 2†</td>
<td>5 ± 3</td>
<td>8 ± 3</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>90</td>
<td>0.9 ± 0.2</td>
<td>1.5 ± 3</td>
<td>6 ± 2†</td>
<td>2 ± 2</td>
<td>5 ± 3</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>120</td>
<td>0.7 ± 0.2</td>
<td>-2 ± 2</td>
<td>6 ± 2†</td>
<td>0 ± 2</td>
<td>4 ± 2</td>
<td>2 ± 2</td>
</tr>
</tbody>
</table>

Q-EG interval = interval from the onset of the QRS complex in the limb lead ECG to the intrinsic deflection of the bipolar electrogram recorded in the infarcted and normal zones; Q-EG-1 through Q-EG-5 intervals were determined from the innermost pair of bipolar electrodes on the intramyocardial electrode in the infarcted zone (Q-EG-1) through the outermost pair (Q-EG-5). Values are means ± SE; % change = mean percent change from control value before lidocaine was administered.

* P < 0.01
† P < 0.05
Table 1 lists the results obtained during and after the lidocaine infusion for each of the following determinations: serum lidocaine concentration, Q-EG intervals in the infarcted zone, i.e., Q-EG-1, Q-EG-2, Q-EG-3, Q-EG-4, and Q-EG-5, Q-EG intervals in the normal zone, QRS duration, and effective refractory periods of the infarcted and normal zones. The results are expressed as mean percent changes ± SE from control values for each determination at each indicated time during and after the lidocaine infusion.

**SERUM LIDOCAINE CONCENTRATION**

The serum lidocaine levels during the study are listed in Table 1 and shown in the top curves in Figures 2 and 3. At 5 minutes, the mean serum lidocaine level was 5.3 μg/ml. Subsequently, levels declined to a mean of 2.35 μg/ml at 30 minutes and then slowly rose to reach a steady state of 3.1-3.3 μg/ml between 60-120 minutes of the lidocaine infusion. These steady-state serum lidocaine concentrations were within the range of 2-5 μg/ml that is considered to be therapeutic (21). On discontinuing the lidocaine infusion, serum lidocaine levels fell (top curves, Figs. 2 and 3).

**CONDUCTION INTERVALS**

The Q-EG intervals recorded in the infarcted zone were consistently prolonged by the lidocaine infusion. An example of the change in the Q-EG interval for a representative pair of electrodes in the infarcted zone (in this instance the Q-EG-5 interval) during and after lidocaine infusion is shown in Figure 2. The shape of the curve showing changes in the Q-EG-5 interval in the infarcted zone closely resembles the curve showing serum lidocaine concentration. There was an early prolongation of the Q-EG-5 interval in the infarcted zone, reaching 11% at 15 minutes; then there was a decline to an 8% prolongation at 30 minutes, and later, between 60-120 minutes of the lidocaine infusion, there was a steady prolongation of the Q-EG-5 interval of 17-18%. At this time the steady-state serum lidocaine level was 3.1-3.3 μg/ml.

The prolongations of the Q-EG intervals during and after lidocaine infusion at the other four bipolar electrode sites in the infarcted zone (Table 1) were similar in direction and magnitude to those shown for the Q-EG-5 interval in Figure 2; they also followed the directional changes in serum lidocaine concentration. The initial rapid intravenous bolus injection of lidocaine caused an early 11-17% prolongation of Q-EG intervals in the infarcted zone which reached its peak in 10-15 minutes. At 30 minutes, the prolongation of Q-EG intervals in the infarcted zone declined along with the serum lidocaine concentration. Between 60-120 minutes of the lidocaine infusion, when there was a steady-state serum lidocaine level of 3.1-3.3 μg/ml, there was a steady prolongation of Q-EG intervals at all five bipolar electrode sites in the infarcted zone of 17-26%.

The prolongation of Q-EG intervals in the infarcted zone during lidocaine infusion was statistically significant for all electrode sites. After completion of the lidocaine infusion, Q-EG intervals declined at all recording sites in the infarcted zone; this decline again paralleled the serum lidocaine levels.

The Q-EG interval of the normal zone did not change significantly (Fig. 2) except for a mean prolongation of 1.5% 5 minutes after the rapid intravenous bolus injection of lidocaine. This prolongation probably resulted from the high blood levels of lidocaine which existed for a brief period immediately after

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The initial intravenous bolus injection. The QRS duration in the recorded limb lead ECG did not change significantly throughout lidocaine infusion (Fig. 2), a finding consistent with results of previous studies on canines and humans (21).

There was no significant change in the sequence of the electrograms recorded through the intramyocardial electrodes in the infarcted left ventricular wall during or after lidocaine infusion. This finding suggests that lidocaine caused a uniform slowing of the spread of activation in the infarcted zone. Slight adjustments in gain settings of the recording apparatus were made during the study so that we could accurately time the intrinsic deflection of the recorded electrograms; thus, we could not determine whether lidocaine caused any change in the size of the electrograms recorded in the infarcted zone.

EFFECTIVE REFRACTORY PERIOD

Lidocaine caused a prolongation of the effective refractory period in the infarcted zone (Fig. 2, Table 1) but with a different time course than that of the Q-EG prolongation. During the first 30 minutes of lidocaine infusion, there was a prolongation of 4-5% in the effective refractory period in the infarcted zone, but this change was not statistically significant. Between 45-120 minutes of lidocaine infusion, there was a statistically significant stepwise prolongation of the effective refractory period in the infarcted zone which amounted to 10% at 45 minutes and 23% at 120 minutes. After the lidocaine infusion had been discontinued, the effective refractory period in the infarcted zone gradually decreased, but the prolongation still remained statistically significant for another 60 minutes.

Lidocaine did not cause a significant change in the effective refractory period of the normal tissue (Fig. 2, Table 1); in other words, the effect of lidocaine on the effective refractory period of the normal zone differed from its effects on the effective refractory period of the infarcted zone. An important result of this different effect of lidocaine in the two zones is shown in Figure 3. The top trace shows the serum lidocaine levels; the bottom trace shows the average difference (in msec) between the mean effective refractory period of the normal zone and that of the infarcted zone before, during, and after lidocaine infusion. Before lidocaine administration, the mean effective refractory period of the normal tissue was 26 msec longer than that of the infarcted zone, a finding consistent with previous observations that have shown a shortening of the effective refractory period caused by acute myocardial infarction (19). This disparity in refractoriness gradually declined to 1 msec at 120 minutes of the lidocaine infusion. The disparity in refractoriness between normal and infarcted zones increased again to 27 msec by 120 minutes after the lidocaine infusion had been discontinued.

Discussion

In this study we showed that in delaying ventricular activation and prolonging the effective refractory period lidocaine has different effects on infarcted zones and normal zones of the in situ heart. Most previous studies on lidocaine's antiarrhythmic effect have dealt with alterations in the transmembrane potentials of individual cardiac cells studied by microelectrodes (7, 11, 12). Because lidocaine in therapeutic concentrations did not reduce the \( V_{\text{max}} \) of canine Purkinje fibers or ventricular muscle, one classification of antiarrhythmic agents placed lidocaine in a different group from other local anesthetics (8). However, because of a drug-induced depression of \( V_{\text{max}} \) in the rabbit atrium, another classification placed lidocaine in the same group with local anesthetic antiarrhythmic agents (22). The variability in these studies and the differences between the effects of lidocaine on infarcted zones in the present study and those reported in microelectrode studies on normal tissue demonstrate that drug-induced changes in electrical activity of isolated non-depressed cardiac cells might not adequately reflect changes in the in situ heart or in abnormal infarcted tissue within the heart. The delay in ventricular activation and the prolongation of the effective refractory period in infarcted zones found in the present study clearly show that lidocaine has "local anesthetic" properties on infarcted tissue of the in situ heart.

Reasons for Lidocaine's Different Effect on Normal and Infarcted Tissues

Although some microelectrode studies...
have found that lidocaine does not have local anesthetic properties when it acts on ventricular muscle or Purkinje fibers at therapeutic concentrations (7, 11, 12), certain local anesthetic effects have been found at higher concentrations considered to be toxic. In Purkinje fibers the maximum rate of rise of the action potential is slowed, and in ventricular muscle refractoriness is prolonged (7, 11, 12). A potentiation of lidocaine’s local anesthetic effects could thus explain our observation that, when it acts on ischemic tissue, lidocaine delays activation and prolongs refractoriness. Characteristics of infarcts that could potentiate the effects of lidocaine include lower pH (23–26), higher extracellular potassium concentration (23, 24, 27), local accumulation of certain metabolites (28), or a different reactivity of infarcted tissue to lidocaine that is independent of the extracellular milieu.

Local pH within infarcted or ischemic zones of the heart is lower than that in normal zones. At a lower pH a greater proportion of lidocaine is in the ionized form, an effect which is prominent because the physiological range of pH (7.35–7.45) is close to the pKa of lidocaine (7.86) (29). In studies on nerve membranes, it has been shown that the ionized form of lidocaine is the active local anesthetic but that it is the unionized form which passes through intact nerve cell membranes (30). For an infarcted cell, it seems likely that the ionized lidocaine would still be the active local anesthetic form. However, because of a change in permeability of cell membranes in the infarcted zone, both the unionized and the ionized form of lidocaine might enter the cell at similar rates. A higher local level of ionized lidocaine would mean that a greater amount of the more active form of lidocaine would be present (30–32), which in turn could cause lidocaine to have local anesthetic effects.

The higher extracellular potassium levels in infarcted zones could also explain lidocaine’s different effect on infarcted normal zones. Elevated potassium levels enhance the effect of local anesthetic antiarrhythmic agents on $V_{\text{max}}$ of Purkinje fibers (33). In the case of lidocaine, one study has shown that at high potassium levels (5.6 mM) it reduces $V_{\text{max}}$ but at lower potassium levels (3.0 mM) the same concentrations of lidocaine do not influence $V_{\text{max}}$ (34). High potassium levels caused by cellular disruption in infarcted zones (23, 24, 27) could thus cause lidocaine to have local anesthetic actions.

Another possibility for the potentiation of lidocaine’s local anesthetic action on infarcted zones is that metabolites, such as adenine nucleotides or lactic acid, which are in high local concentrations in infarcted zones, could modify its action. However, this effect has not yet been demonstrated.

Finally, it could be that the only reason for lidocaine’s different effect on the infarcted zone is the altered ultrastructure of the infarcted cells; the extracellular milieu might be less important.

DISTRIBUTION OF LIDOCAINE

The distribution and the time course of delivery of lidocaine to the infarcted zone of the heart have previously received little attention, but they might be important in understanding lidocaine’s antiarrhythmic effect. Following occlusion or ligation of a coronary artery, the movement of lidocaine into the infarcted zone might be similar to that found for other substances in the canine heart; it could involve diffusion from the left ventricular cavity (35), diffusion from normal myocardium (27), or passage via collateral or other intact blood flow to the infarcted zone (36). Two of these three routes of distribution would deliver lidocaine to the infarct slowly. On the other hand, the endocardium receives lidocaine by direct diffusion from the adjacent left ventricular cavity with a rapid time course (33). In this way, lidocaine could quickly reach the Purkinje system which in canines and also in humans is situated at or near the endocardium. This distribution of lidocaine could explain the observation (Fig. 2) that the prolongation of Q-EG intervals in the infarcted zone consistently occurred with a rapid time course after the administration of lidocaine, although the prolongation of the effective refractory period in the infarcted zone occurred with a much slower time course. Since the Purkinje system is situated at or near the endocardium and since rapid diffusion of lidocaine from the left ventricular cavity to the endocardium can occur, it seems likely that lidocaine’s effect in delaying ventricular activation in the infarcted zone was mediated by its effect on the Purkinje system. On the other hand, the deep
layers of the myocardium, which are more dependent on supply from adjacent normal myocardium and collateral blood flow, are more slowly perfused (36). Our measurement of effective refractory period in the infarcted zone was made through electrodes in the deep layers of the myocardium. Thus, the slow time course of lidocaine's effect of prolonging the effective refractory period in the infarcted zone could be explained by delayed delivery of the drug to the deep layers of the myocardium in the infarcted zone.

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