The Effects of Lidocaine on Intracellular and Extracellular Potentials, Activation, and Ventricular Arrhythmias during Acute Regional Ischemia in the Isolated Porcine Heart

RENE CARDINAL, MICHEL J. JANSE, IVO VAN EEDEN, GUY WERNER, CHRISTOPH NAUMANN D'ALNONCOURT, AND DIRK DURRER

SUMMARY We studied the effects of lidocaine, 1 and 5 µg/ml, on subepicardial transmembrane and DC extracellular potentials and on spontaneous ventricular arrhythmias during occlusion of the left anterior descending coronary artery in the Langendorff-perfused porcine heart. In the minutes following coronary occlusion, the resting membrane potential and action potential amplitude of cells in the ischemic zone were reduced and the extracellular complexes displayed TQ depression and ST elevation. The magnitude of the depression in action potential amplitude and of the ST elevation was exaggerated and their time course was accelerated during occlusion in the presence of lidocaine. Diastolic potentials were little affected by the drug. The activation delay and the number of sites that failed to be activated in the ischemic zone were increased by lidocaine. The effect of drug on normal tissue was to decrease the action potential duration. These drug effects were concentration-dependent. Lidocaine did not prevent ventricular tachycardia from occurring during occlusion. However, the high concentration prevented its degeneration into fibrillation. Patterns of activation characteristic of a "focal" mechanism, possibly due to the injury current flow and present at the onset of tachycardia, were not affected by lidocaine. The drug did not entirely prevent but greatly decreased the incidence of large circus movements (diameter 1-2 cm) taking place in the ischemic zone and responsible for continuation of tachycardia. However, the high concentration prevented the fractionation of wavefronts into multiple wavelets and micro-reentrant circuits (diameter: 0.5 cm) which is characteristic of fibrillation. The effectiveness of lidocaine against fibrillation during coronary occlusion is due to conversion of areas of unidirectional block and slow conduction in the ischemic zone into areas of total block. Circ Res 49: 792-806, 1981

MALIGNANT ventricular arrhythmias occur spontaneously within minutes after experimental coronary occlusion. Studies from several laboratories indicate that their mechanism is reentry in the ischemic myocardium (Elharrar and Zipes, 1977; Lazzara et al., 1978; Janse et al, 1980). Maps of the distribution of extracellular potentials in the ischemic zone and neighboring normal areas of the isolated porcine heart have shown that large potential gradients are present between normal and ischemic tissue and that these gradients generate "injury currents" of a large magnitude across the ischemic border. We have presented evidence that this injury current may constitute an additional mechanism for arrhythmogenesis in myocardial ischemia by inducing "focal" activity on the normal side of the ischemic border, possibly in Purkinje fibers (Janse et al., 1980). The presence of several distinct mechanisms of arrhythmogenesis possibly offers different approaches for attempts to prevent or suppress these arrhythmias.

Lidocaine is the antiarrhythmic drug most commonly administered to patients with acute myocardial infarction. However, many uncertainties remain about the effectiveness of lidocaine and its mechanism of action against ventricular arrhythmias after experimental coronary occlusion (Epstein et al., 1974; Hope et al., 1974; Borer et al., 1976) and very early in the clinical course of acute myocardial infarction (Pantridge and Adgey, 1969; Lie et al., 1974; Adgey and Webb, 1979).

The purpose of the present study was: (1) to use intracellular microelectrode and DC extracellular techniques in order to gain insight into the electrophysiological actions of lidocaine during coronary occlusion in the isolated porcine heart, and (2) to study the effect of lidocaine on the spontaneous ventricular arrhythmias and the underlying pat-
terns of activation to determine whether one or another of the mechanisms of arrhythmogenesis are affected by this drug.

Methods

Seventeen pigs weighing 20-25 kg were premedicated with atropine sulfate (0.02 mg/kg, i.m.) and azaperone* (12 mg/kg, i.m.). Anesthesia was induced by administration of metomidate* (4 mg/kg, i.v.) and maintained by administration of sodium pentobarbital (15 mg/kg, i.v.). The thorax was opened by a midsternal incision. After administration of heparin (3 mg/kg, i.v.), 1.5 liters of blood were collected by means of a needle inserted into the superior vena cava while 1 liter of modified Tyrode’s solution was being infused into a femoral vein. The heart then was removed and fixed to the Langendorff method. A detailed description of the perfusion system and the composition of the perfusion medium (K+ = 4.5 mm) have been reported previously (Downar et al., 1977; Janse et al., 1980).

The heart was driven at a rate faster than the spontaneous frequency of the sinus node by bipolar stimuli applied by means of a pair of electrodes fixed to the right atrium. In a few experiments in which coronary occlusion produced AV block, the driving electrodes were attached to the right ventricle. Each heart was driven at either a slow or a fast rate throughout the experiment (basic cycle length of 450 or 300 msec, respectively).

Ischemia of the anterior portion of the left ventricular wall and septum was produced by clamping the anterior descending branch of the left coronary artery within a few millimeters of its bifurcation from the circumflex branch. Occlusions lasted 15 minutes and were followed by a period of reperfusion of at least 15 minutes. Either three or four occlusions were done in each heart: the first two occlusions were always done in the absence of drug; the third occlusion was done in the presence of lidocaine 1 or 5 µg/ml. Whenever the low concentration was tested during the third occlusion, a high input impedance buffer amplifier. A DC amplifier with differential input measured the potential at this electrode with respect to a relative zero reference potential recorded by a wick electrode fixed to the aortic root.

Transmembrane potentials were recorded by means of floating glass microelectrodes (Woodbury and Brady, 1956) filled with 3 M KCl in contact with a chlorided silver wire which was connected to a high input impedance buffer amplifier and a differential DC amplifier. The microelectrode resistance ranged from 10 to 30 MΩ. Impalements were done by means of a hydraulic micromanipulator. A second microelectrode with a broken tip was positioned within less than 1 mm of the first and served as extracellular reference.

The output of the differential amplifier used to measure extracellular and transmembrane potentials was connected to an Ampex multichannel instrumentation FM tape recorder. The signals were printed out on an Elema multichannel inkwriter. In three out of a total of five experiments, acceptable intracellular recordings were obtained during successive occlusions. In one of these, mapping of extracellular potentials was performed as well.

Mapping the Distribution of Extracellular Potentials and the Sequence of Activation

Extracellular potentials were recorded from multiple epicardial sites on the anterior portion of the left ventricular wall in the area supplied by the occluded vessel and also on its posterolateral portion in the area supplied by the circumflex artery. In three experiments, intramural electrodes (Janse et al., 1979) were used to record DC extracellular potentials from the subepicardium and intramural sites 4 and 8 mm underneath the subepicardium. In the early stage of this study, the extracellular complexes were recorded sequentially from the multiple sites by means of a single wick electrode. (Seven experiments: three without drug, four with lidocaine). A thin rubber membrane was perforated to obtain a grid of 50 to 75 holes 0.7 mm in diameter and separated by 2 mm. The potentials were recorded by touching the epicardial tissue underlying a hole lightly with the cotton wick. Potentials could be recorded from all sites within 2 or 3 minutes. Amplitudes of DC potentials at fixed intervals of the cardiac cycle and activation times were measured by hand from signals printed out at a sensitivity of 1 mV/mm and a speed of 100 mm/sec, yielding a precision of 10 msec/mm. Maps of potential amplitudes and activation times could be

* Azaperone (R1929; Stresnil) is a butyrophenone tranquilizer, and metomidate (R7315; Hypnodd) is an ultrashort-acting nonbarbiturate hypnotic. Both drugs were purchased from Janssen Pharmaceutica, Beerse, Belgium.
achieved using this method only during a stable rhythm. Results obtained with this technique are shown in Figures 1, 3, and 4.

Four experiments were done by means of a technique that allowed us to record 60 extracellular potentials simultaneously and therefore to map, in addition to the pattern during stable rhythm, the activation sequence during spontaneous arrhythmias in which the pattern of excitation changed from beat to beat. Multiple electrodes consisted of 60 cotton wick electrodes with their tips glued to a perforated rubber sheet, the wicks protruding through the holes of the sheet. The sheet could be sutured to the epicardial surface. The interelectrode distance was usually 5 mm and signals were recorded over most of the ischemic zone and also from closely neighboring normal, nonischemic, regions. The exact distribution of electrodes is described in Results. After an initial 20-fold amplification by a high impedance, low pass (cutoff frequency, 40 Hz) 60-channel amplifier, the signals were led into a high-speed multiplexing A/D converter [maximal sampling frequency 130 kc/sec (Micro Consultants VHF mod 15)]. Samples were taken every 8 msec and written into a circular buffer. During the experiment, one of the signals was displayed on a Megatek graphic display. During normal rhythm or when an event occurred (spontaneous premature beats, ventricular fibrillation), a button could be pushed so that the signals of the preceding 2 seconds were transferred to a high-speed digital tape recorder (Kennedy 9300) under the control of a PDP-11-34 computer. Analysis of the data was performed through use of the same computer by means of an interactive program in which the signals were displayed in groups of five on the Megatek graphic display, and the moments of activation were indicated on the screen with a joystick. Activation was manifest as an intrinsic deflection in the extracellular signal, and sites that failed to be activated during ischemia displayed monophasic extracellular signals. Zero potentials were obtained from preocclusion recordings, and DC potential values could be obtained from signals recorded during coronary occlusion at any desired moment of the cardiac cycle. The potential level during the ST segment was measured at a fixed point in the cardiac cycle, which varied in the different experiments from 250 to 330 msec after the atrial stimulus artifact. This point was chosen in such a way that it occurred after the intrinsic deflection of the local electrograms recorded from the ischemic zone. Thus, the ST potential was measured at a moment when the ischemic cells were in their plateau phase, and the nonischemic cells were either in their plateau phase, or because they were activated much earlier, had started to repolarize. Values of activation times and DC potentials were printed out, and isochrone and isopotential maps were made by hand. (For detailed description of the recording system, see van Capelle et al., 1979.)

Results

Reproducibility of Changes in Electrical Activity Produced by Multiple Coronary Occlusions in the Absence of Drug

Figure 1 shows the reproducibility of TQ depression and ST segment elevation after 12 minutes of coronary occlusion in four occlusions in the absence of drug in the same heart. Prior to each occlusion,
TABLE 1 Effects of Lidocaine on Ventricular Arrhythmias during Coronary Occlusion and Reperfusion

<table>
<thead>
<tr>
<th></th>
<th>No drug 1st (13)</th>
<th>No drug 2nd (13)</th>
<th>Lidocaine 5 μg/ml (13)</th>
<th>Lidocaine 1 μg/ml (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT-occl.</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>VT-VF-occl.</td>
<td>9</td>
<td>8</td>
<td>1*</td>
<td>2</td>
</tr>
<tr>
<td>VT-VF-reperf.</td>
<td>6*</td>
<td>12</td>
<td>11</td>
<td>7</td>
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Numbers in parentheses = number of hearts in each group. In 13 hearts, occlusions were done twice in the absence of drug and then in the presence of lidocaine, 5 μg/ml. In seven of these, an additional occlusion was done with 1 μg/ml in each heart, the occurrence of each type of arrhythmia in a given occlusion was taken as whether or not it occurred, regardless of how many times it did in the particular occlusion. The values in the table are the number of hearts in which each type of arrhythmia occurred. VT = ventricular tachycardia (more than three consecutive ventricular premature beats), the arrhythmia ending spontaneously; VT-VF = ventricular tachycardia which degenerated into ventricular fibrillation (arrhythmias not spontaneously terminating). occl during occlusion; reperf immediately following reperfusion.

the TQ and ST segments were within 3 mV of the zero potential line (not shown). As previously reported (Kleber et al., 1978), coronary occlusion produced depression of the TQ segment below the zero line and elevation of the ST segment above the line in the area supplied by the occluded vessel (sites 1-5). In contrast, the sites located on the lateral wall of the heart (sites 6-8) essentially were unaffected by occlusion or else displayed slight ischemic changes (site 6) or a reversal in polarity (site 8). It is clear that the magnitude of TQ depression was similar at all corresponding sites of all four occlusions. The magnitude of the ST elevation also was similar at corresponding sites during occlusions 2, 3, and 4, but it was consistently smaller during the first occlusion. Activation times of these sites (not shown) were also shorter in the first than in subsequent occlusions. Four occlusions were done in the absence of drug in three other experiments. After 12 minutes of occlusion, the TQ depression was similar in all four occlusions, whereas the ST deviation was consistently smaller in the first than in the three subsequent occlusions. In three experiments, ventricular fibrillation occurred upon reperfusion after each of the four periods of occlusion. In one experiment, ventricular fibrillation occurred during occlusion, and this arrhythmia occurred in all four occlusions. Thus, the incidence of these arrhythmias was predictable between occlusions in these four hearts. The occurrence of any type of arrhythmia in a given occlusion was tabulated in terms of whether it occurred or not, regardless of how often it occurred in a particular occlusion (see Table 1).

Therefore, we adopted the following protocol to obtain control measurements and to study the effects of lidocaine thereon in individual hearts: the first two occlusions were done in the absence of drug; the values obtained during the second occlusion were used as control values. The third occlusion was done in the presence of lidocaine, 1 or 5 μg/ml. Whenever the low concentration was tested during the third occlusion, a fourth occlusion was done in the presence of 5 μg/ml.

Effects of Lidocaine on Myocardial Electrical Activity during Coronary Occlusion

Figure 2 shows the effects of lidocaine on intracellular and extracellular potentials simultaneously recorded prior to and during occlusion at a site in the center of the ischemic zone. The recording site remained constant throughout the different occlusion periods.
sions. Under control conditions, the resting membrane potential was -90 mV and the transmembrane action potential had an amplitude of 100 mV and a duration 300 msec prior to occlusion. With time during occlusion, the resting potential and the upstroke of the transmembrane action potential were progressively reduced and the action potential duration shortened. The TQ segment was depressed below the zero line. However, the extracellular potential recorded at this site did not display ST segment elevation. At 10 and, more strikingly, at 12 minutes, there was an alternation in action potential amplitude and duration which was reflected in the alternation of the ST segments. Activation was also progressively more delayed during occlusion.

In the presence of lidocaine, the transmembrane resting potential and action potential amplitude recorded from the same cell prior to occlusion were similar to those under control conditions (-90 mV and 100 mV). However, the action potential duration was much shorter (less than 250 msec). It was possible to obtain reliable transmembrane recordings during successive occlusions in two other experiments; in these experiments lidocaine reduced the action potential duration by about 10 msec prior to occlusion. The TQ and ST segments were at zero potential. Occlusion in the presence of lidocaine produced qualitatively the same effects as under control conditions. However, the depression of the action potential upstroke and the shortening of its duration, together with the increase in activation delay, had an accelerated time course of development and were also exaggerated. On the other hand, the degree and time course of the reduction in resting potential and of the TQ depression were similar to changes under control conditions. The low concentration of drug also was tested in this experiment. It produced effects that were similar but less intense than those produced by the high concentration.

Figure 3 illustrates the effects of lidocaine on the epicardial potential distribution during diastole (TQ) and systole (ST) and also on the pattern of activation. The lefthand portion of the electrode was overlying the ischemic zone on the anterior wall of the heart, while its righthand portion extended laterally over the normal zone. In all four occlusions, the extracellular potentials recorded at sites progressively deeper into the ischemic zone displayed an increasing degree of TQ depression and ST elevation and were activated progressively later. In agreement with our reproducibility studies, the ST elevation and activation delay in the ischemic zone were less during the first than during the second occlusion done in the absence of drug. Also, a few sites that had been responsive during the first occlusion were no longer responsive during the second. The TQ depression at some sites in the ischemic zone was accentuated obtained -16 mV in the presence of the high concentration of lidocaine. The low concentration of drug did not affect the distribution of systolic potentials, but the high concentration clearly extended the areas where ST elevation was maximal. The low concentration of lidocaine slowed activation over the ischemic zone and extended the area of unresponsiveness. These effects on activation were amplified greatly by the high concentration of drug. Note that the righthand portion of the maps was not affected by the drug. The corresponding portion of the electrode overlies nonischemic regions of the lateral wall which are supplied by the circumflex artery. Thus, the effects of lidocaine on these electrophysiological parameters were restricted to the ischemic zone itself.

Figure 4 summarizes the effects of lidocaine on these parameters in four experiments by showing the differences between their values during occlusion 2, which defines the control values, and occlusion 1 (no drug), occlusion 3 (1 µg/ml lidocaine), and occlusion 4 (5 µg/ml lidocaine). Two experi-
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FIGURE 4  Effects of lidocaine on TQ and ST potentials (upper right- and lefthand graphs), activation time and the number of sites which failed to be activated (lower right- and lefthand graphs) after 12 minutes of occlusion. The data are presented as differences between the values obtained during the second occlusion and each of the other occlusions as indicated on the abscissa. The mean (±SE) of the differences obtained at each site of a multiple electrode are plotted on the ordinate. In all experiments, occlusions 1 and 2 were done in the absence of drug. The dots joined by full lines show the pooled data from three experiments in which occlusions 3 and 4 were also done in the absence of drug. The triangles and 3 crosses joined by broken lines show the data from experiments in which occlusions 3 and 4 were done in the presence of 1 and 5 µg/ml of lidocaine; the triangles and crosses are used to distinguish the drug studies done at a basic cycle length of 450 (two experiments) and 300 msec (two experiments), respectively. Note the increase in lidocaine in ST elevation, activation delay, and number of sites failing to be activated.

ments were conducted at a fast rate (cycle length 300 msec, broken lines connecting unfilled triangles), and two experiments at a slower rate (cycle length 450 msec, crosses connected by broken lines). Also shown are the pooled data from three experiments in which 4 successive occlusions were performed in the absence of lidocaine (filled dots, connected by solid lines, driving cycle length 450 msec). Only data were used that were derived from recordings made from sites which, during occlusion 2, had a TQ potential level of −2 mV, or more negative values. On the average, the TQ potential during occlusion 2 was about −10 mV, the ST potential was elevated beyond 10 mV, activation was delayed by about 60 msec compared to preocclusion values, and a minimum of 2 to 10 sites failed to be activated among the 35 to 55 ischemic sites recorded from in each individual experiment. For every occlusion, the values were subtracted algebraically from the corresponding value during occlusion 2. Thus, a positive change in TQ potential difference means less TQ depression, a positive change in ST potential difference means more ST elevation. Likewise, positive changes in activation time and number of blocks mean more activation delay and more inexcitable sites.

In agreement with the data of Figure 1, the ST elevation during the first occlusion was significantly less than during the control (second) occlusion. Activation delay was also significantly less in occlusion 1 than in occlusion 2, as was the number of inexcitable sites. At the lower driving rate, ST elevation, activation delay and the number of unresponsive sites were increased by lidocaine. At the fast driving rate, there was no effect on ST elevation; an increase in the number of inexcitable sites occurred only at the high concentration of drug, but a very marked increase in activation delay was observed at both concentrations. This difference in drug action at the two driving rates might be due to two factors: (1) at the fast rate, the number of inexcitable sites is already large in the control situation; (2) the marked activation delay in the ischemic zone will tend to decrease ST elevation, since the nonischemic myocardium is already repolarizing. Surprisingly, the differences in TQ potential in the lidocaine experiments were statistically different from zero; this was true not only for occlusions 3 and 4, but also for occlusion 1, in which no drug was present. This, and the fact that there was no consistent progressive effect on TQ potentials when the lidocaine concentration was increased, suggests that the differences of 0.5 to 3 mV might be due at least partly to baseline shifts, rather than to drug action.

In four experiments, in which 60 electrograms were recorded simultaneously, data were stored in the computer from occlusion 2 (control) and occlusion 3, in which in this series a concentration of lidocaine of 5 µg/ml was used.

Figure 5 shows the values obtained at different times during occlusion under control conditions and in the presence of drug in a representative experiment. After only 2 minutes of occlusion, the TQ segment already was depressed at many sites. From 2 to 3 minutes of occlusion, there was an abrupt increase in TQ depression and activation time, both under control conditions and in the presence of drug. However, at any given degree of TQ depression, the activation was more delayed in the presence of drug than under control conditions, and a few sites failed to be activated. After 6 minutes of occlusion, most sites displaying TQ depression under control conditions were still activated with great delay, whereas, in the presence of lidocaine, most of these sites failed to be activated. After 12 minutes, many sites have become inexcitable in the
FIGURE 5 Effects of lidocaine on the relationship between the activation time and the extracellular potential during the TQ segment at several times during coronary occlusion. A multiple electrode recorded extracellular potentials simultaneously from 60 sites in the ischemic zone and the neighboring nonischemic regions. Its configuration was the same as shown in Figure 6. The earliest activation in the area under the recording electrode took place in the same region under all conditions and was taken as zero time. The upper part of the graphs obtained after 3, 6, and 12 minutes of occlusion shows sites at which the extracellular complexes were monophasic, indicating the absence of activation. Note that at similar levels of TQ depression, sites are either activated with greater delay (as compared to control) or failed to be activated after 3 minutes of occlusion in the presence of drug. At 6 minutes, most sites displaying TQ depression failed to be activated in the presence of drug while still being activated with great delay under control conditions. Basic cycle length = 300 msec. At 12 minutes, many sites have become inexcitable in the control occlusion, but the number of inexcitable sites is greater in the presence of lidocaine.

Effects of Lidocaine on Spontaneous Ventricular Arrhythmias during Coronary Occlusion and Reperfusion

We investigated the influence of this drug on spontaneous ventricular arrhythmias during coronary occlusion. Figure 6A shows the arrhythmias occurring during the control occlusion. During the normal paced rhythm, the extracellular potentials recorded in the ischemic zone displayed TQ-ST displacement, whereas the potential recorded on the right ventricle had isoelectric TQ and ST segments. The second lead from the top of the figure displayed the characteristic alternation of the polarity of T waves (Kleber et al., 1978). Both premature beats occurred during the negative displacement of the T waves. The second premature beat was followed by an extremely rapid ventricular tachycardia which degenerated into ventricular fibrillation. Normal paced rhythm was restored by application of a DC countershock 30 seconds later. The normal rhythm was maintained until reperfusion after 15 minutes of occlusion induced VF immediately (not shown).

Figure 6B shows that, in the presence of lidocaine in the same heart, alternation in the polarity of the T wave also occurred at the same site as during the control occlusion. The first beat of an episode of ventricular tachycardia also occurred during the negative displacement of the T wave. The first and fourth leads also displayed alternation of the polarity of the T wave during the tachycardia. However, this arrhythmia spontaneously converted to the normal paced rhythm. Ventricular fibrillation did not occur during occlusion in the presence of the drug, despite several runs of ventricular tachycardia (defined as three or more consecutive ectopic beats). However, reperfusion after 15 minutes of occlusion immediately induced ventricular fibrillation, as under control conditions.

Table 1 summarizes the effects of lidocaine on ventricular arrhythmias during coronary occlusion.
and reperfusion. Three types of arrhythmias were observed consistently in the absence of drug: (1) early episodes of ventricular tachycardia during occlusion (3 or more consecutive ectopics) which would terminate spontaneously or degenerate into ventricular fibrillation, (2) ventricular fibrillation, and (3) ventricular tachycardia upon reperfusion, which always degenerated into ventricular fibrillation. During the control occlusion, these arrhythmias respectively occurred in 3, 2, and 4 of 5 hearts in which the driving cycle was 450 msec; and in 8, 6, and 8 of 8 hearts in which the driving cycle was 300 msec (yielding an overall incidence of 11, 8 and 12 hearts, as shown in Table 1 for the second occlusion). These numbers show that all arrhythmias occurred more frequently at the fast than at the slow driving rate. All episodes of ventricular tachycardia and fibrillation occurring during occlusion appeared between 2.5 and 4 minutes at the fast driving rate and between 4 and 6 min at the slow rate. These episodes were recurrent for 2 or 3 minutes and then usually subsided. The arrhythmias due to reperfusion appeared within a very few beats of release of the occlusion.

Table 1 shows that there was no difference in the incidence of ventricular tachycardia and fibrillation occurring between the first and second occlusions. However, the incidence of ventricular fibrillation was greater upon reperfusion after the second than after the first occlusion. Lidocaine did not affect the incidence of ventricular tachycardia during occlusion and ventricular fibrillation upon reperfusion. However, the high concentration of lidocaine, but not the low, significantly reduced the incidence of ventricular fibrillation occurring during occlusion. Indeed, this arrhythmia occurred only once in 13 occlusions done in the presence of the high concentration of drug as compared to 8 times in the 13 control occlusions. This single episode of fibrillation during occlusion in the presence of drug occurred in a heart that was driven at the high rate.

Figure 7A shows patterns of activation under control conditions during a spontaneous arrhythmia very similar to that shown in Figure 6A. In the very first beat of the tachycardia, two premature wavefronts propagated from the periphery of the electrode where it was overlying border regions (see map of diastolic potentials in this figure), swept into the ischemic zone, and collided at its center. A basically similar pattern of activation was found in the next four beats of the tachycardia. However, islands of block were appearing, around which there were unsuccessful attempts at circus movement. The patterns of activation of the following beats are unknown because the period of registration had ended (see Methods). When registration resumed at the 12th beat, the pattern of activation (not shown) was more complex. In this beat and the following two, areas of block of greater dimensions were present (diameter 1-2 cm), and there were attempts at circus movements around these areas. However, the circus movements mapped out by means of the epicardial leads were not complete. The first complete circus movement that could be mapped out at the epicardial level occurred at beat 15 (not shown, but similar to middle diagrams in Fig. 7B). Its diameter was about 1.5 cm and the revolution time 115 msec. In the following beats, the sequence of activation indicated attempts at circus movements of similar dimensions, although again the complete circuits could not be mapped out at the epicardium. We have shown previously the possibility of intramural circus movements during tachycardia (Janse et al., 1980). Complete circus movements were mapped out during beats 20 and 25, with revolution times of about 100 msec and 65 msec, and diameters over 1.5 cm and less than 1 cm,
FIGURE 7 Effects of lidocaine on activation maps during spontaneous ventricular arrhythmias. The upper righthand part of the figure shows an anterolateral view of the heart in the area supplied by the anterior descending and circumflex branches of the left coronary artery. DC extracellular potentials were recorded simultaneously from 60 sites, as indicated in the diagram. Isopotential lines during the TQ segment after 3 minutes of occlusion are also indicated. A: 3 min 15 sec of occlusion under control conditions. First ectopic of ventricular tachycardia (VT): zero time is Q wave of preceding basic beat (atrial drive at basic cycle length = 300 msec). Middle maps (arbitrary zero time): maps of 26th and 27th ectopics—VT degenerating into fibrillation (VF). B: 2 min 40 sec of occlusion in the presence of 5 μg/ml of lidocaine. First ectopic: zero time is Q wave of preceding basic beat. Middle maps (arbitrary zero): maps of 35th and 36th ectopics during VT. Last beat (54th) of VT is shown at extreme right.

respectively. The middle diagrams in Figure 7A show the sequence of activation in the next beats. The activation pattern consisted of a complete circus movement around an area of block with a diameter less than 1 cm and also multiple wavelets sketching out incomplete circus movements of even smaller dimensions. This pattern of fractionated activity was characteristic of fibrillation and, once established, it maintained itself until electroconversion. A DC shock was applied 10 seconds later.

Figure 7B shows patterns of activation during a spontaneous tachycardia in the presence of lidocaine, 5 μg/ml, in the same heart. The first diagram shows that the very first beat of the tachycardia in the presence of drug displayed a pattern of activation similar to that during the control occlusion, i.e., wavefronts propagated from the periphery of the electrode over border regions and collided at the center of the ischemic zone. However, there already were areas of block, and conduction in the ischemic zone was slower in the presence of drug, although the tachycardia occurred slightly earlier than under control condition (2 min 40 sec instead of 3 min 15 sec). The five following beats had similar patterns, and, again, a few beats were missed between periods of registration. The 14th beat displayed a large but incomplete circus movement with a diameter of about 1.5 cm. In the following beats, there were many attempts at large circus movements (diameter 1–2 cm) all of which failed to be completed. Ectopic activity was maintained all along by wavefronts propagating from the periphery of the electrode over border regions. Once again, possibility of intramural circus movements could not be discarded. A complete circus movement could be mapped out on the epicardium for beat 29 (diameter about 1 cm and revolution time 154 msec), and another for beat 35. The middle diagrams in Figure 7B show the activation sequence during beats 35 and 36. A wavefront propagating from the area under the apical part of the electrode was blocked on its way into the ischemic zone and then conducted in the border and nonischemic regions in a counter-clockwise fashion. This wavefront completed a full revolution, reexcited sites proximal to the initial block, and then was blocked (at least on the epicardium) after almost another half revolution. This circus movement was similar to the complete circus movement shown in the middle diagrams in Figure 7A. However, no multiple waves were present in the presence of drug, in contrast to control conditions. In the presence of lidocaine, the activation maps displayed large circus movements only (diameter of 1 cm or greater), whether they were complete or not. Figure 7B also shows the sequence of activation of the last beat of the tachycardia (54th beat). Again there was an attempt at a large circus movement which was interrupted after only one-half revolution. Immediately thereafter, there was electrical silence and the normal paced rhythm resumed shortly after.

Figure 7 suggests that lidocaine may not affect the mechanism of initiation of the tachycardia or abolish large circus movements, but that it may prevent the fractionation of wavefronts into multiple wavelets, thereby preventing fibrillation. In the three experiments in which activation maps were made during arrhythmias, and in which ventricular tachycardia occurred both in the control situation (occlusion 2) and in the presence of lidocaine, 5 μg/ml (occlusion 3), we attempted to quantify the occurrence of reentry. The results are shown in
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Figure 8 Effects of lidocaine on the degree of distal delay required for reexcitation proximal to a site of block. The upper diagrams show the method of measurement. A wavefront was blocked along one route (bars indicate conduction block). The letter p indicates a site just proximal to the site of block and d a site distal to it. Case a: (circus movement reentry): the same wavefront was then conducted through other regions and produced activation at site d. Case b: (multiple wavefront reentry) activation at d was produced by a different wavefront than the one blocked at site p. Intervals p-d between activation at p prior to block and later activation at d were measured during tachycardia in a control occlusion, in the presence of lidocaine, 5 µg/ml, and also during reperfusion in the presence of drug. The circles indicate values obtained when activation at d did not produce reexcitation at p. Triangles are values when reexcitation of p did occur; in the reperfusion arrhythmia, the open triangles are used to distinguish the values obtained in late beats from those obtained in the early beats (up to 15th beat; full triangles). The mean ± SE and number of observations are indicated for each set of data. The asterisk indicates a significant difference (Student's t-test, P < 0.01) from the value when reexcitation did or failed to occur were similar (87 ± 8 msec and 86 ± 5 msec, respectively). During the tachycardia in the presence of lidocaine, the degree of delay across the area of block required for reexcitation to occur (116 ± 10 msec) was greater than during the control occlusion (86 ± 5 msec). These values were significantly different (P < 0.01). The third part of Figure 8 shows the values of the p-d interval obtained during the tachycardia caused by reperfusion in the presence of drug. In those cases, the tachycardias degenerated into ventricular fibrillation. In contrast, during the ventricular tachycardia always resulted in VF. At the beginning of the tachycardia (filled triangles), an even greater degree of delay was required to produce reexcitation (139 ± 8 msec). However, in later beats of the tachycardia (unfilled triangles: 16th beat or later), the degree of delay required for reexcitation (88 ± 8 msec) was reduced to a value very similar to that during the control occlusion. These lower values were obtained after more than 10 seconds of reperfusion. Thus, there was a reduction of the antifibrillatory action of the drug as the tissue quickly recovered upon reperfusion. Table 1 clearly showed that lidocaine did not prevent ventricular fibrillation occurring upon reperfusion, in contrast to fibrillation occurring during occlusion.

While measuring the values shown in Figure 8, we also measured the interval p-p' between activation at p prior to block and the subsequent activation p' at this site during tachycardia. Combining all data, this coupling interval was significantly shorter when reexcitation from the distal site was successful (130 ± 5 msec; n = 46) than when it failed (211 ± 6 msec; n = 100; P < 0.01). Thus, ectopic beats generated by reentry were more closely coupled than those resulting from an alternative mechanism. When reexcitation by a wavefront propagating from the distal site did occur, the coupling interval p-p' was significantly greater during occlusion in the presence of drug (152 ± 9 msec; n = 7) than during the control occlusion (119 ± 5 msec; n
any given heart, the measurements obtained during superfused fibers. In any case, the sine qua non much faster in the intact perfused heart than in the electrophysiological alterations in ischemia, our gested that lysophosphoglycerides may contribute to the electrophysiological alterations as in the present study resulted in a rapid normalization of the intracellular action potential configuration, as well as of the TQ and ST segment potentials and a return to baseline levels of high energy phosphate compounds within a 15-minute period of reperfusion. The data reported in the present study indicate that the electrophysiological parameters were indeed reproducible during the second, third, and fourth occlusions in the absence of drug. However, the degree of ST elevation, activation, and number of sites failing to be activated in the ischemic zone were less in the first occlusion. The reason for this difference is not clear. It could be argued that metabolic or neural factors are released in the ischemic myocardium during the first occlusion, and that depletion of their sources would make their concentration less in subsequent occlusions. Conversely, factors could be released, only partially washed out upon reperfusion, and accumulate in subsequent occlusions. It has been suggested that lysophosphoglycerides may contribute to the electrophysiological alterations in the ischemic myocardium (Sobel et al., 1978; Corr et al., 1979). However, the rapid reversal of these alterations upon reperfusion in our preparations contrasts with the slow reversibility of the depressant effects of these compounds on the action potential of Purkinje fibers superfused in the tissue bath. Therefore, if lysophosphoglycerides do indeed contribute to electrophysiological alterations in ischemia, our data show that the reversal of these changes is much faster in the intact perfused heart than in the superfused fibers. In any case, the sine qua non condition for a self-controlled study was fulfilled: in any given heart, the measurements obtained during the second occlusion could be used as control values for those which were then obtained in the presence of lidocaine during the third and fourth occlusions.

In our experiments, lidocaine produced either slight or no change in the intracellular resting membrane potential and the extracellular potential during the TQ segment in the ischemic myocardium. Arnsdorf and Sawicki (1979) have reported that lysophosphatidylcholine reduces the cardiac membrane potassium conductance and resting membrane potential. In contrast, lidocaine is reported to increase the membrane potassium conductance (Arnsdorf and Bigger, 1972; 1975). Thus, if lysophosphoglycerides or any other substance had contributed to the depression of the electrical activity during ischemia in addition to an altered transmembrane ionic distribution, lidocaine should have produced a hyperpolarization of the cell membrane and, therefore, a reduction of the TQ depression recorded in the ischemic zone. We have observed a reduction of the TQ depression by a few mV during occlusion in the presence of drug in many experiments. However, we feel that it might have been due at least partially to shifts in the reference potential and that, therefore, our data are in this respect rather inconclusive and of limited usefulness with regard to whether the reduction in resting membrane potential in myocardial ischemia could be attributed to the presence of another factor in addition to hyperkalemia.

The present study shows that lidocaine administered prior to coronary occlusion exaggerates the depression of the intracellular action potential amplitude and accelerates the time course of this depression in the minutes following coronary occlusion. The corresponding drug effect on the DC extracellular potentials consisted of an increase in the magnitude of ST elevation. Lidocaine also further increased the activation delay as well as the number of sites failing to be activated in the ischemic zone. These drug effects were restricted to electrical activity recorded in the ischemic zone. The only drug effect on the configuration of transmembrane action potentials recorded in normal tissue was a reduction of the action potential duration, in agreement with studies on preparations consisting of normal cardiac tissues and at normal extracellular potassium concentrations (Obayashi et al., 1976). There was no extension by the drug of the area where occlusion produced depression of the electrophysiological parameters. The overall increase in ST elevation was not due to a shift of the electrophysiological border zone. This emphasizes the need to distinguish between the effects of a drug on transmembrane potentials and its possible effects on the actual area of ischemic myocardium in the assessment of "infarct size" by TQ-ST segment mapping techniques (Holland and Brooks, 1977). Selective depression by lidocaine of conduction in ischemic tissue has been reported previously within minutes of coronary occlusion (Kupersmith,
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1979), 2 hours (Kupersmith et al., 1975), and 3 days (El-Sherif et al., 1977) after experimental coronary occlusion. In these studies, conduction was expressed as the interval from the onset of the QRS complex to activation at bipolar recording sites and was further depressed by the drug in the ischemic or infarcted zone but not in the normal zone. These observations are consistent with our own.

It still is not known whether activity in the ischemic zone consists of depressed fast response or slow response activity. Brennan et al. (1978) have recently reported that lidocaine reduces the maximum upstroke velocity and conduction velocity of depressed fast response action potentials which were produced in the tissue bath by elevating the potassium concentration in the perfusate to the point at which the resting membrane potential was reduced to around $-60 \text{ mV}$, but without abolishing excitability. The drug produced these effects without affecting the resting membrane potential. In contrast, lidocaine had little or no effect on slow response action potentials produced by perfusing the fibers in a Na$^+$-free, Ca$^{2+}$-rich solution or a high K$^+$ solution containing norepinephrine. Accordingly, the effects of lidocaine on the electrical activity in the ischemic zone described in the present study are consistent with a further drug-induced depression of the fast inward sodium current independent of change in the resting potential. Chen et al. (1975) have demonstrated in guinea pig ventricular muscle that lidocaine alters the voltage dependence and slows the recovery kinetics of the fast sodium current in such a way as to decrease $(dV/dt)_{max}$ as the diastolic membrane potential is reduced below $-80 \text{ mV}$. These actions of lidocaine may explain the selectivity of its depressant effect on the fast inward sodium current in ischemic as compared to normal tissue, since membranes in the ischemic zone are depolarized to a diastolic potential between $-60$ and $-80 \text{ mV}$ (Kleber et al., 1978). Hondeghem and Katzung (1977) have proposed a model for the interaction of local anesthetic-like antiarrhythmic drugs with cardiac fast sodium channels which provides several possible mechanisms for the selective depression of the fast inward current in depolarized tissue by these drugs.

The increase caused by lidocaine of the activation delay and the number of sites failing to be activated in the ischemic zone may not result entirely from the further depression by the drug of the fast inward sodium current. In addition to its dependence on the active generator properties of the membrane, conduction of an action potential depends on passive membrane properties, and it can also be influenced by the excitability of the membrane (Dominguez and Fozzard, 1970). The relevant passive factors are the specific myoplasmic resistance and the membrane capacitance, to both of which the conduction velocity is inversely related. Arnsdorf and Bigger (1975) found in long sheep Purkinje fibers superfused in vitro with normal Tyrode’s solution that these passive properties were not affected by lidocaine in the same concentration as used in the present study. However, they found that it reduces myocardial excitability by decreasing d.c. input resistance and membrane resistance, and by decreasing the membrane length constant. The depression of excitability by lidocaine under the experimental conditions used by Arnsdorf and Bigger needs not result in a reduction of the propagation velocity of the action potential, since the local circuit currents responsible for propagation in normal myocardium are several-fold above the threshold requirements. However, this depression of excitability by lidocaine also could be expected to contribute to the increase in activation delay and the propensity for block in ischemic myocardium, since the strength of the local circuits then is certainly less as a result of the depression of the active generator properties of the membrane. These depressant actions of lidocaine previously have been postulated to form the basis of its antiarrhythmic effects against reentry in acutely ischemic myocardium (Kupersmith, 1979) and in the late myocardial infarction period (El-Sherif et al., 1977) by conversion of a one-way block into a two-way block in the reentrant pathway. However, it has been difficult to demonstrate directly this mechanism of drug action.

Effects of Arrhythmias: Reentry

Studies from several laboratories have indicated that reentry is a mechanism of arrhythmogenesis in the minutes following experimental coronary occlusion (Elharrar and Zipes, 1977; Lazzara et al., 1978). We have recently reported that large circus movements in the ischemic region (diameter: 1-2 cm) are responsible for the late beats of episodes of ventricular tachycardia and that fragmentation of these wavefronts into multiple wavelets of smaller dimensions is responsible for the degeneration of tachycardia into fibrillation (Janse et al., 1980). In the present study, we found that lidocaine did not prevent the large circus movements, although they could be mapped out much less frequently in the presence of drug than during control occlusions. In the presence of lidocaine, the tachycardia stopped spontaneously when a large circus movement failed to be conducted. On the other hand, lidocaine prevented the fragmentation of wavefronts into multiple wavelets which was characteristic of fibrillation under control conditions. During occlusion in the presence of drug, the ischemic tissue’s availability for re-excitation was reduced and the degree of delay required to do so was increased. Since lidocaine depresses both the active generator properties (fast inward current) and the excitability of membranes in the ischemic zone (see above), these drug effects may be interpreted as though only large circus movements could be conducted by the is-
myocardial tissue in the presence of the drug.

Also, lidocaine accelerated the time course of the depression of the action potential upstroke. In our preparations, runs of ventricular tachycardia and fibrillation appeared after about 3 minutes of occlusion when greatly delayed activation took place at many sites in the ischemic zone, and then receded after the 6th minute when sites in the ischemic zone were no longer activated. In addition to increasing the number of sites which failed to be activated, lidocaine accelerated the transition from depressed conduction to failure of activation in the ischemic zone. These drug effects support the concept that lidocaine abolished reentry by converting areas of unidirectional block and slow conduction into areas of total block.

On the other hand, the activation delay in some areas of the ischemic zone where conduction persisted in the presence of lidocaine could be much greater than under control conditions. This slowing of conduction, together with an extension of the area of total block, fulfilled the conditions for circus movements, and they could indeed occur in the presence of drug. The only instance of fibrillation in the presence of the drug occurred when there was a minimal increase in the area of block together with a large increase in delay. It has been suggested that, in low concentrations, lidocaine may promote reentry by slowing conduction without producing bidirectional block in reentrant pathways (Gamble and Cohn, 1972; Darby et al., 1972). In our experiments, the low concentration of lidocaine (1 µg/ml) did not increase the incidence of ventricular arrhythmias, but neither did it provide the protection against ventricular fibrillation occurring during occlusion which was afforded by the high concentration (5 µg/ml). This observation emphasizes that the effectiveness of lidocaine is concentration-dependent and supports recommendations that high blood levels of lidocaine must be maintained in the early phase of acute myocardial infarction if protection is to be achieved (Lie et al., 1974).

In contrast to fibrillation occurring during occlusion, lidocaine failed to prevent fibrillation occurring upon reperfusion. Cells in the ischemic zone recover quickly upon release of the coronary occlusion, and as the tissue recovers the selective depression of conduction by lidocaine should be expected to disappear. Consequently, the tissue in the ischemic zone becomes increasingly more available for reentrant excitation, thereby setting the stage for fibrillation. Thus, the failure of lidocaine to abolish ventricular fibrillation upon reperfusion might have been due to the fact that arrhythmias then occurred during improvement of the electrical activity, rather than during depression of the electrical activity in the ischemic zone which took place upon occlusion.

Effects on Arrhythmias: “Focal” Activity

We have recently proposed that a “focal” mechanism, possibly induced by injury current flow across the ischemic border, is responsible for single premature beats and the initial beats of tachycardia, and that it might be induced in Purkinje fibers on the normal side of the ischemic border (Janse et al., 1980). In the present study, we found that lidocaine did not prevent the occurrence of the pattern of activation which is characteristic of this mechanism, nor the initiation of episodes of ventricular tachycardia. At least three mechanisms could be considered to possibly account for this focal activity: (1) enhancement of normal phase 4 depolarization in Purkinje fibers; (2) enhancement of abnormal automaticity (or sustained rhythmic activity) at low levels of membrane potential; (3) direct stimulation by the injury current. The failure of lidocaine to suppress this “focal” mechanism in the present study makes it unlikely that it consists of the first of these mechanisms, since lidocaine is well known to suppress normal phase 4 depolarization in Purkinje fibers (Bigger and Mandel, 1970; Arnsdorf and Bigger, 1972). As to the second mechanism, lidocaine has been reported to suppress, also, the triggered sustained rhythmic activity at low levels of membrane potential which is occasionally seen in Purkinje fibers with otherwise normal membrane properties and bathed in physiological Tyrode’s solution (Arnsdorf, 1977). On the other hand, lidocaine did not affect rhythmic activity at low levels of membrane potential which was induced by depolarizing current pulses in guinea pig papillary muscle (Imanishi et al., 1978) and in strands of porcine Purkinje fibers (C. Naumann d’Alnoncourt, R. Cardinal, and M.J. Janse, unpublished observations). In the experiments of Arnsdorf, the Purkinje fibers spontaneously remained at a low level of membrane potential where the rhythmic activity was generated. An increase in membrane permeability to K⁺ by lidocaine could then produce the transition to the normal resting potential, thereby abolishing the rhythmic activity. In contrast, the cell membrane was maintained at a low level of potential by an external current source in the experiments of Imanishi et al. and our own. This experimental procedure may more closely simulate the situation of the cell membrane under the influence of the injury current.

Previous studies have considered the effects of lidocaine on spontaneous ventricular arrhythmias within minutes of experimental coronary occlusion in the anesthetized or conscious dog. Hope et al. (1974) reported that lidocaine did not prevent ventricular tachycardia. Borger et al. (1976) showed that lidocaine in concentrations varying between 1.2 and 5.5 µg/ml significantly reduced the incidence of ventricular fibrillation (control 14/16; lidocaine 5/11 dogs). These observations are consistent with our own that lidocaine does not prevent ventricular tachycardia but reduces the incidence of fibrillation. In these in situ or in vivo cardiac preparations, the coronary blood flow depends on cardiac output. Ventricular tachycardia in these preparations certainly reduces the cardiac output and coronary
blood flow, thereby possibly extending the ischemic damage to other areas of the heart and precipitating ventricular fibrillation. In contrast, coronary blood flow is not dependent on cardiac pump function in our isolated Langendorff-perfused hearts, and, thus, lidocaine may be expected to be more effective in preventing ventricular fibrillation in our preparations than in hearts in situ. This must also be taken into account in giving clinical perspective to our study.

Lidocaine's effectiveness against ventricular arrhythmias in the very early stage of acute myocardial infarction in patients is unclear. In a group of patients treated in a coronary care unit within 6 hours of the onset of symptoms, lidocaine prevented ventricular fibrillation but did not abolish "warning arrhythmias" and ventricular tachycardia (Lie et al., 1974). This is consistent with our experimental study in which lidocaine prevented ventricular fibrillation but not runs of tachycardia occurring during occlusion. On the other hand, data collected by mobile coronary care units (Adgey and Webb, 1979) have indicated that lidocaine may not be as effective against out-of-hospital ventricular fibrillation. Adgey and Webb emphasized the deleterious influence of autonomic disturbances which may override the beneficial effects of the drug in these patients, and they stated that the effectiveness of lidocaine is reduced in the presence of sinus tachycardia. It is noteworthy in this respect that the only instance of ventricular fibrillation in the presence of 5 μg/ml of lidocaine in the present study occurred while the heart was driven at the fast rate.

Inasmuch as our model may simulate events taking place in the very early phase of myocardial ischemia in humans, one might expect that both reentry and injury current flow across ischemic borders may contribute to the generation of arrhythmias in these patients. The present study shows that only the former mechanism is affected by lidocaine, and then is not entirely abolished. It may be important to develop approaches to prevent or suppress the component of arrhythmias due to the flow of injury current.

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