Effect of Lidocaine on the Ventricular Fibrillation Threshold in the Dog during Acute Ischemia and Premature Ventricular Contractions

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SUMMARY

The effect of lidocaine on the ventricular fibrillation threshold was investigated in the anesthetized open-chest dog during paced supraventricular rhythm, during acute ligation of the anterior descending coronary artery, and during premature ventricular contractions. The minimum current (in milliamperes) required to induce ventricular fibrillation was determined by passing a train (100 Hz) of 10–14 constant-current pulses through ventricular epicardial electrodes during the vulnerable period of the cardiac cycle. Lidocaine was administered intravenously either as a sudden injection or as a "loading" injection followed by a constant infusion. Following a single injection of 0.7 mg/kg the blood lidocaine decreased to half its original arterial concentration in 9 min. After the termination of a 50–60-min constant drip of 70 μg/kg/min which was preceded by a loading injection of 2 mg/kg, the blood lidocaine concentration fell to 50% of its original value in 31 min. Lidocaine at therapeutic blood levels (1.2–5.5 μg/ml) increased the fibrillation threshold during paced supraventricular rhythm and reversed the fall in fibrillation threshold accompanying acute myocardial ischemia and premature ventricular contractions. The present studies quantify the ability of lidocaine to reduce the vulnerability of the heart to fibrillation during supraventricular rhythm, acute ischemia, and premature ventricular beats and provide information concerning the metabolism of lidocaine in the anesthetized dog.

Additional Indexing Words:
Ischemia Vulnerability Antiarrhythmia agent Defibrillation Myocardial infarction Sudden cardiac death

The technic of passing current through epicardial electrodes during early diastole in order to test the vulnerability of the ventricle or its tendency to undergo fibrillation was first described by Wiggers and Wegria.1 In their investigations of vulnerability, Han et al.2–4 determined that a decrease in the ventricular fibrillation threshold is associated with those factors which increase the degree of nonuniformity of recovery of excitability of ventricular muscle and predispose the heart to reentry. These same factors are those associated clinically with a greater risk of fibrillation. Lidocaine is an important drug in the management of patients following acute myocardial infarction.5,6 While it is accepted that lidocaine does inhibit the occurrence of postinfarction tachyarrhythmias,7 there is some doubt as to whether it has
a direct effect on the myocardium which increases the fibrillation threshold. Bacaner reported that lidocaine had a negligible effect on the fibrillation threshold while Shinohara reported positive results. In neither of these studies, however, was the blood lidocaine concentration monitored during the fibrillation threshold determinations. In the present studies the blood lidocaine concentration was monitored while the ventricular fibrillation threshold was determined during paced supraventricular rhythm, during acute ischemia, and during premature ventricular beats.

Methods

The experiments were performed on 21 dogs, of both sexes, anesthetized with sodium pentobarbital (30 mg/kg). The animals were maintained by positive-pressure ventilation at a minute volume determined from a body weight nomogram. The lead II electrocardiogram (ECG) was monitored throughout the experiments. Control experiments demonstrated that open-chest animals can be maintained for 5 hours in acid-base balance as long as the fibrillation procedures are carried out at 10-min or longer intervals. Open-chest dogs which showed progressive metabolic acidosis also showed a progressive decrease in ventricular fibrillation threshold (VFT). In all of the present experiments data were obtained from animals which exhibited control VFT which did not vary by more than 10% for 45 min to 1 hour before each experimental manipulation. For data to be acceptable the VFT had to return to control value after the experimental manipulations. Lidocaine was administered through a femoral venous catheter, and arterial samples for blood lidocaine determinations were obtained from the abdominal aorta through an indwelling femoral catheter. Lidocaine whole-blood concentrations were determined as lidocaine hydrochloride monohydrate using the gas chromatographic technic. Lidocaine was administered either in a single sudden injection (0.7 mg/kg) or in a constant drip infusion (70 μg/kg/min) following a loading injection (2 mg/kg). The drip infusion was terminated after 50–60 min. The heart was exposed by a midsternal thoracotomy and was suspended in a pericardial sling. Bipolar stimulating electrodes were secured to the right atrium, and the sinus node was crushed to permit pacing the heart at a constant basic cycle length of 380 msec for all experiments.

The ventricular fibrillation threshold (VFT) was determined by passing a gated train of impulses through bipolar electrodes sutured on the right or left ventricle during the vulnerable period of the T wave of the ECG. The electrodes (1 mm in diameter) were embedded in an acrylic plaque which maintained their separation at 5 mm. The fibrillation pulses were 4 msec in duration and occurred at 10-msec intervals (100 Hz). There were 10–14 of these pulses in the train. They were synchronized to the atrial stimulus and delivered after every twelfth ventricular response during the threshold determinations. The current delivered was measured directly by recording the voltage drop across a precision 1 kohm resistor in series with the electrodes. The VFT was defined as the minimum current in milliamperes (mA) which induced fibrillation. When fibrillation ensued, the heart was immediately defibrillated using a capacitor discharge DC defibrillator. The placement and duration of the fibrillating train in each case started within the absolute refractory period of the beat to be tested and did not extend beyond the absolute refractory period of the ventricular beat evoked by the train. The analog data of figure 1 demonstrates this for a paced supraventricular beat (A) and for a premature ventricular contraction (B). The heart was allowed to recover for 10–15 minutes following each determination.

In the experiments in which the threshold for fibrillation was measured following a premature ventricular beat, the premature beat was evoked after every 12 normal beats by a single 4-msec stimulus through the same ventricular electrodes used for determining the fibrillation threshold. The premature ventricular beat was the earliest that could be evoked with a current of twice threshold intensity delivered during the relative refractory phase of the preceding normal beat. The fibrillating train of pulses was then gated to occur during the vulnerable period of the premature ventricular beat.

In other experiments the threshold for fibrillation was determined during acute coronary occlusion. Occlusion was reversibly attained in the main left anterior descending coronary artery or one of its large branches using a snare applied around the vessel near its base. The fibrillating electrodes were sutured onto the left ventricle. The electrodes were placed so that they would be within the ischemic area during the occlusion. For each fibrillation threshold determination during acute ischemia the coronary occlusion lasted less than 2 min. The heart was allowed to recover for 10–15 min following each determination.

Results

Blood Lidocaine Levels following an Intravenous Injection and following a Constant Infusion

Figure 2 compares the time courses of the disappearance of lidocaine from the blood following a sudden injection of 0.7 mg/kg (A)
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Figure 1

Analog data demonstrating the placement of the train of pulses used to test ventricular fibrillation threshold (VFT) are presented. (A) The procedure for testing the VFT for a paced supraventricular beat. (B) The procedure for testing a premature ventricular beat (PVC). The rapid phases in the records have been retouched. ECG = lead II electrocardiogram; RV = right ventricular epicardial electrogram recorded approximately 4 mm from the fibrillating electrodes; S = the stimulus signal which indicates the timing of the stimulus evoking the premature ventricular response (P), and the fibrillating train of pulses (F). T represents timing signals occurring at 100-msec intervals. On the left of A, the relationship of the fibrillating train to the T wave in the ECG and in the local electrogram (RV) is shown; on the right, the result of passing current through the fibrillating electrode is presented. Notice that, although the fibrillating train does evoke a response, the train still does not extend beyond the absolute refractory period of the evoked response. On the left of B, the fibrillating train (F) is positioned across the T wave of a stimulated PVC. On the right of B, during the passage of current through the fibrillating electrodes, the train does not extend beyond the absolute refractory period of the evoked response.

and following the termination of a constant infusion of 70 μg/kg/min (B). In A, the log of the arterial blood lidocaine concentration is plotted against time following a single intravenous injection of lidocaine in seven dogs. To allow time for intravascular mixing, the first arterial samples were drawn after 1 or 2 min. The initial blood concentrations ranged between 6.3 and 1.3 μg/ml. The regression line at the Y intercept in A was 2.7 μg/ml, and it fell to 50% of this value in 9 min. Virtually all of the lidocaine was removed from the blood within 30 min after the injection. In B of figure 2, blood lidocaine concentrations are plotted against time following the termination of a constant infusion of intravenous lidocaine in four dogs. In these dogs an intravenous "loading dose" of 2 mg/kg was given first; this
was followed by a constant infusion of 70 µg/kg/min for 50–60 min. The first arterial samples ranging between 3.0 and 1.0 µg/ml were obtained immediately after the termination of the infusion. Notice that the time course for the disappearance of lidocaine from the blood for the dogs in B is much longer than for those in A. In B the half-time for the disappearance of lidocaine was 31 min.

**Effect of Lidocaine on the VFT**

In each of five animals studied, the VFT for normal beats was increased following either a single injection of lidocaine or a constant infusion of lidocaine. The mean maximum increase in the fibrillation threshold above control was 32.0 ma ± 10.9 (sd). Figure 3 compares the time course of changes in the VFT with the time course of changes in the blood lidocaine concentration following a single 0.7-mg/kg injection in a representative experiment. The VFT increased from an average control value of 45 ma to 67 ma following the administration of lidocaine, and the time course of the changes in VFT correlated with the changes in blood lidocaine concentration. Figure 4 is a similar experiment in which a constant infusion of lidocaine was administered. In this case, the VFT increased from an average control value of 35.7 ma to a maximum of 68 ma during the lidocaine infusion. The prolonged time that the VFT was elevated correlated with the prolongation of the elevation in blood lidocaine concentration. Therefore, following either an injection or an infusion, the time courses of the fibrillation threshold changes correlated with the lidocaine concentration changes.

The late phase of the time course of the change in VFT in figure 4 exhibits an “undershoot” before its return to control value. This phenomenon is also shown in figure 3. It was also observed in the premature ventricular contraction experiments to be described later. The “undershoot” occurred in four of nine animals in which the time courses were determined. The phenomenon appears to be real; however, its cause is unknown.

Studies by other investigators have shown that the VFT is decreased (the heart is easier
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VENTRICULAR CONTRACTIONS. The control thresholds are shown at the left of the figure; their mean value was 31.8 ± 8.6 ma. The fibrillation thresholds were decreased by 68.5% following the premature ventricular contractions as can be seen at time zero (mean 10.0 ± 3.6 ma) in figure 5. Lidocaine was then administered as a loading injection followed by a constant infusion in these dogs. The VFT following PVCs was redetermined at 30 and 60 min after the beginning of lidocaine administration. Notice that the fibrillation thresholds following the PVCs were increased during the administration of lidocaine. The mean values were 28.3 ± 14.5 ma at 30 min and 23.2 ± 10.7 ma at 60 min. The corresponding mean blood lidocaine levels for the four dogs at 30 and 60

to fibrillate) following premature ventricular contractions and following acute ischemia.4, 10, 11 Since both of these conditions can occur during acute myocardial infarction it was of interest to determine the effect of lidocaine on the fibrillation threshold under these conditions. Figure 5 demonstrates the effect of lidocaine on the VFT following experimental premature ventricular contractions (PVC) in four dogs. The fibrillation electrodes were located on the anterior epicardial surface of the right ventricle. After control fibrillation thresholds were determined during paced supraventricular rhythm, the VFT was measured following premature

Figure 3
A comparison of the time course of changes in the normal fibrillation threshold and blood lidocaine concentration following a single intravenous injection of lidocaine (0.7 mg/kg). The control fibrillation threshold at time zero is the average of three values, which did not vary by more than 3 ma.

Figure 4
A comparison of the time course of changes in the normal fibrillation threshold and blood lidocaine concentration following a loading injection of 2.0 mg/kg followed by an intravenous infusion of 70 μg/kg/min of lidocaine. The infusion was terminated at 47 min. The control fibrillation threshold at time zero is the average of three values which did not vary by more than 3 ma.
minutes were 5.8 ± 3.5 and 3.2 ± 1.6 μg/ml, respectively.

Figure 6 demonstrates the effect of lidocaine on the VFT during acute coronary artery occlusion in six dogs. The fibrillating electrodes were located within the region of the left ventricle supplied by the coronary artery which was to be occluded. At the left of the figure the control fibrillation thresholds are shown. Their mean value was 53.0 ± 3.8 ma. During acute ligation of the anterior descending coronary artery the VFT decreased by 52.3% to a mean value of 24.8 ± 3.9 ma (values at time zero in fig. 7). A single injection of lidocaine was then given in each case and the fibrillation thresholds were redetermined during acute occlusion at 4 and 14 min after the administration of lidocaine. Notice that at 4 min after the administration of lidocaine, the mean VFT during ischemia was increased to 56.9 ± 13.2 ma, and at 14 min the mean value was 52.1 ± 13.7 ma. The corresponding blood lidocaine concentrations were 3.3 ± 2.4 μg/ml at 4 min and 1.3 ± 0.7 μg/ml at 14 min after the injection of lidocaine.

In order to determine more precisely the time course of the effects of a single injection of lidocaine on the VFT following ischemia, two series of ischemic VFT determinations were performed in the same animal following injections of lidocaine given 2 hours apart. The data were then pooled to construct figure 7. The VFT determinations for the two runs were staggered in time following the injections so that the pooled data produced experimental points at shorter time intervals than could be practical during a single run. The data of figure 7 show that the time course of the changes in the ischemic fibrillation threshold follows closely the time course of the changes in blood lidocaine concentration following an intravenous injection.

**Figure 5**

The effect of lidocaine on the fibrillation threshold during premature ventricular contractions (PVC). The control fibrillation thresholds are shown at the left. The values at time zero are the fibrillation thresholds during PVCs before lidocaine was administered. The fibrillation thresholds for PVCs during lidocaine administration (loading injection of 2.0 mg/kg followed by an infusion of 70 μg/kg/min for 60 min) are shown at 30 and 60 min. The lines connect data points for the same animals.

**Figure 6**

The effect of lidocaine on the fibrillation threshold during acute coronary artery occlusion (acute ischemia). The control fibrillation thresholds are shown at the left. The values at time zero are the fibrillation thresholds during acute ischemia before lidocaine was administered. The fibrillation thresholds during acute ischemia following lidocaine administration (single injection of 0.7 mg/kg) are shown at 4 and 14 min. During each ischemic threshold determination coronary artery occlusion lasted for less than 2 min. The lines connect data points for the same animals.
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A comparison of the time course of changes during ischemia of the fibrillation threshold and blood lidocaine concentration following a single intravenous bolus (0.7 mg/kg). The fibrillation threshold data points were obtained during two runs in the same animal. During each ischemic threshold determination, the coronary artery occlusion lasted for less than 2 min.

A comparison of figures 5 and 6 presents an additional phenomenon of interest. The control VFT determinations are different in these figures. This difference is related to the experimental protocol. The VFT measurements of figure 5 were obtained on the right ventricle and those of figure 6 on the left ventricle. The higher fibrillation threshold of the left ventricle compared to the right ventricle was first reported by Shumway. In our study of 54 control right ventricular fibrillation threshold determinations in 10 dogs, and 41 control left ventricular determinations in eight dogs, the right ventricular threshold was 23.2 ± 9.2 ma and the left was 51.8 ± 4.3 ma.

Discussion

Lidocaine rapidly diffuses throughout the body tissues following intravenous administration. The liver is the principal site of the metabolism of lidocaine in man. Following relatively large intravenous lidocaine infusions in man, the blood concentration decreases with a half-time of 30 or 40 min. Figure 2 demonstrates that the blood concentration of lidocaine decreases at a more rapid rate following a single injection than following the termination of a constant infusion. The lower blood concentration following a single injection is primarily a result of its dilution as it diffuses from the vascular space to the body tissues; some metabolism also occurs. During a constant infusion, the blood lidocaine has time to equilibrate with the body tissues, and its disappearance from the blood is related primarily to its rate of metabolism. This is supported by the fact that the disappearance of lidocaine in figure 2B behaves more as a monoexponential \( r = 0.819 \) , while in figure 2A its time course of disappearance is more complex \( r = 0.617 \). However, in either case the effects of lidocaine on the ventricular fibrillation threshold (VFT) correlated with the blood lidocaine level.

Figures 3 and 4 demonstrate that lidocaine increases the VFT during paced supraventricular rhythm, and that the time course of the effect is related to the time course of the blood lidocaine concentration. The effect appears immediately after lidocaine administration and rapidly diminishes as the blood lidocaine concentration decreases. Bacaner’s findings that lidocaine’s effect on the VFT is negligible are probably related to the rapid disappearance of lidocaine from the blood following a single injection. In his experiments, the fibrillation thresholds were measured at least 30 min after the injections, at a time when the blood levels must have been greatly reduced.

Following premature ventricular contractions, there is an increase in the degree of dispersion of recovery of the myocardial tissues, and consequently a decrease in the
VFT. Figure 5 demonstrates the decreased fibrillation threshold accompanying PVCs. Even during premature ventricular contractions, lidocaine still increased the fibrillation threshold. Therefore, not only does lidocaine inhibit the occurrence of tachyarrhythmias as has been described clinically, but it also has a direct effect on the myocardium and prevents the increased vulnerability to fibrillation which is associated with premature ventricular contractions.

Shumway and Han reported that the ventricular fibrillation threshold is decreased during acute ischemia. Figures 6 and 7 demonstrate the decrease in VFT found in our experiments during ischemia. Note also that lidocaine more than reverses the decrease in VFT during acute ischemia, and that the time course of the effects are related to the time course of arterial blood lidocaine concentration. All of the effects described for lidocaine occurred within the therapeutic dose range (1.2–5.5 mg/ml) for this drug.

An occasional PVC in a heart which is otherwise free of myocardial disease is usually not serious even when it falls on the T wave of a preceding beat; i.e., experience in patients with failing pacemakers and during catheter pacing of the heart have shown that PVCs can be electrically evoked on the T wave of preceding beats without causing fibrillation. The amount of current delivered during artificial pacing in the human heart at normal heart rates is less than is necessary to induce ventricular fibrillation during the vulnerable period of the normal dog heart (20–50 ma). These observations suggest that spontaneous PVCs occurring on T waves are not the only factor involved in the tendency of fibrillation to occur in acute myocardial infarction. There is also recent evidence that fibrillation can occur following myocardial infarction without being induced by a PVC. However, fibrillation appears to be most likely when premature ventricular beats fall on the T waves in hearts which exhibit abnormally large degree of nonuniform recovery in excitability or otherwise exhibit conditions which predispose them to the sustained reentry which precedes fibrillation.

Several recent studies have suggested the electrophysiologic mode of action of lidocaine. Studies using microelectrodes and show that besides diastolic depolarization lidocaine decreases the action potential duration and effective refractory period of Purkinje fibers without affecting action potential amplitude or rate of depolarization. Lidocaine also decreases the dispersion of action potential durations and prevents the occurrence of multiple action potentials following single stimuli. In general, these factors would tend to decrease nonuniform recovery of excitability and decrease the opportunity for reentry to occur. This is undoubtedly related to lidocaine's ability to increase the ventricular fibrillation threshold.

The basis for the threshold undershoot phenomenon during the disappearance of lidocaine is unknown. Whether this is an artifact of the technic cannot be determined from our experiments. It may be that during the disappearance of lidocaine from the cardiac tissues some regions recover from its effects before others and thus make the system transiently more nonhomogeneous and, therefore, more susceptible to fibrillation, than compared to control situations.

Our studies suggest that lidocaine's effectiveness in treating patients with acute myocardial infarction is not only due to its ability to decrease the occurrence of ectopic activity, but also is related to its direct effect on the myocardium decreasing its vulnerability to develop fibrillation.

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