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Regional Myocardial Lidocaine Concentration Determines the Antidysrhythmic Effect in Dogs after Coronary Artery Occlusion

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Ischemic ventricular dysrhythmias were produced in 40 of 47 anesthetized mongrel dogs by high ligation of the left anterior descending coronary artery. Dysrhythmias were treated with a single iv bolus of 20, 40, 80, or 120 mg of lidocaine (L) in order to determine the dose at which approximately 50% of animals had an antidysrhythmic response. Cardiac output and regional myocardial blood flow (RMBF) were measured by using radionuclide labeled microspheres. Lidocaine concentration ([L]) was measured from samples of arterial and venous blood and normal and ischemic myocardium. All dogs treated with 40, 80, or 120 mg of L had an antidysrhythmic effect. However, with 20 mg of L the dysrhythmia persisted in 12 and resolved in 14. With 20 mg of L, ischemic myocardial [L] was greater in dogs with an antidysrhythmic effect than in those with persistent dysrhythmias (1.14 ± 0.12 *vs.* 0.76 ± 0.04 $\mu g \cdot g^{-1}$), but no difference was seen for arterial, venous, and normal myocardial [L]. Ischemic RMBF was higher in the dogs that had an antidysrhythmic effect than in those that did not, 9.8 ± 1.5 *versus* 6.9 ± 1.3% of normal. With 20 mg of L, [L] in ischemic myocardium correlated well with ischemic RMBF. The antidysrhythmic response to L had a threshold at a tissue concentration of greater than or equal to 1.0 $\mu g \cdot g^{-1}$ (chi-square = 8.55, $P < 0.005$). For this model, the [L] in ischemic myocardium during acute ischemia correlates with the antidysrhythmic response to L, while the concentration in normal myocardium or blood does not. (Key words: Anesthetics, local: lidocaine. Complications: dysrhythmia. Heart: dysrhythmia, lidocaine; ventricular tachycardia; treatment; ischemia.)

SINCE ITS INTRODUCTION as a clinically useful antiarrhythmic drug in the 1950s,[1–3] lidocaine has become a primary drug for preventing or treating the ventricular dysrhythmias that complicate acute myocardial infarction. Despite such wide usage, the pharmacokinetics of lidocaine within the myocardium are not well documented. There are substantial differences in both locus and mechanism of ventricular dysrhythmias when those occurring acutely after myocardial infarction are compared with those appearing at a later time. Ventricular dysrhythmias that occur immediately after coronary blood flow is interrupted are thought to originate within the ischemic myocardium and are likely due to reentrant mechanisms within the ischemic epicardium[4]; ventricular dysrhythmias that occur several hours later originate as an ectopic focus in surviving Purkinje fibers on the endocardial surface of the ischemic zone.[5]

Among patients with acute myocardial infarction, both the dose of lidocaine that produces an antidysrhythmic effect and the concentration of lidocaine ([L]) in blood produced by that dose vary widely.[6] Ischemia likely affects the relationship between the plasma concentration and the pharmacologic effect of a drug if the locus of its activity is within an ischemic region and if conditions are not in a steady state, as is the case after a single intravenous bolus of a drug, since regional blood flow determines drug distribution to tissue.[7] For example, myocardial ischemia alters the pharmacokinetics of propranolol, digoxin, and procainamide within the myocardium.[8–10] The present investigation was designed to determine the relationship of the antidysrhythmic effect of lidocaine to its concentration in plasma, normal myocardium, and ischemic myocardium during experimentally induced myocardial ischemia and ventricular ectopy produced by coronary artery occlusion, and to examine the pharmacokinetics of lidocaine in normal and in ischemic myocardium.

Materials and Methods

Forty-seven mongrel dogs of either sex weighing 22.5 ± 5.1 (SD) kg were anesthetized with sodium thiamylal (30 $mg \cdot kg^{-1}$, iv), orotracheally intubated, and mechanically ventilated with room air. Polyethylene catheters were inserted into the right atrium (via the external jugular vein), the common carotid artery, the femoral artery, and the femoral vein to measure arterial pressure, to sample arterial and venous (atrial) blood, and to inject lidocaine. The heart was exposed through a left thoracotomy and suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was

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dissected free from surrounding tissues 0.5 cm distal to its origin, at which point a ligature was placed loosely around the vessel. The left atrium was cannulated through its appendage for subsequent radioactive microsphere injection. Systemic arterial pressure and standard body surface electrocardiogram (lead II) were monitored and recorded continuously on a polygraph (Brush Instruments, Cleveland, Ohio) at a paper speed of 25 $mm \cdot s^{-1}$.

The LAD was occluded by ligation and, 15–30 s after occlusion, 1.5×10^6 9 μm diameter carbonized microspheres (3M Co.) labeled with ^{131}Sn or ^{57}Co were injected into the left atrium to determine regional myocardial blood flow (RMBF) by using techniques previously published.[11] After the development of frequent ventricular ectopy, defined as either ventricular tachycardia or premature ventricular contractions (more than 30% of beats), lidocaine hydrochloride 2% (Astra Pharmaceuticals) was administered as a single intravenous bolus in doses of 20, 40, 80, or 120 mg. These doses were selected arbitrarily for each experiment in order to identify a dose at which approximately an equal proportion of positive and negative rhythm responses occurred. A positive antidysrhythmic effect was defined as a greater than 80% reduction in the frequency of ventricular ectopy or a resolution of ventricular tachycardia.

Samples of blood (arterial and venous) and of myocardium (normal and ischemic) were obtained for analysis of lidocaine concentration ([L]) at times ranging from 30 s to approximately 8 min after lidocaine injection; 8 min was chosen as the outer limit as this time corresponds to approximately five times the initial or redistribution half-time of lidocaine.[12] The amount of myocardial tissue required for analysis precluded more than a single time window for tissue sampling from each individual experimental preparation. After blood was sampled, the ascending aorta was cross-clamped and the heart excised. Transmural samples of myocardium then were obtained to determine [L] and RMBF as described below.

Three samples of normal-appearing (noncyanotic) myocardium were taken from tissue clearly outside the distribution of the occluded vessel, and three samples of ischemic (cyanotic) myocardium were taken from the area clearly within the distribution of the occluded vessel. Each transmural tissue sample was blotted to remove excess blood, weighed, and homogenized in sufficient diluent to make a total homogenate volume of 10 ml; 2-ml aliquots of each homogenized sample were frozen for subsequent lidocaine analysis. The remaining 8 ml were placed in gamma counter tubes to measure radioactive microsphere concentration. Subsequent RMBF calculations were corrected for the amount of tissue homogenate removed for lidocaine analysis.

Lidocaine concentration data and RMBF calculations obtained for the three transmural sites in the normal myocardium were used to calculate a single, "weighted" mean value for transmural lidocaine concentration ($[L]_N$) and for RMBF ($RMBF_N$) in normal myocardium for each animal. The "weighted" mean value was obtained by summing the individual products of tissue sample weight and either $[L]_N$ or $RMBF_N$. This sum then was divided by the sum of the tissue sample weights. In this way the "weighted" mean values reflect both sample weight and [L] or RMBF. Similarly, [L] and RMBF data from ischemic myocardium were used to calculate a single, weighted mean value for transmural lidocaine concentration ($[L]_I$) and RMBF ($RMBF_I$) in ischemic myocardium for each animal. Only tissue samples from the cyanotic region with $RMBF_I$ values less than or equal to 50% of the corresponding $RMBF_N$ were used to calculate $[L]_I$ and $RMBF_I$.

The heparinized blood samples for lidocaine analysis were centrifuged immediately; the plasma fraction was decanted and frozen until analyzed. Lidocaine concentrations in plasma and the myocardial homogenate were determined by gas chromatography by using the method of Keenaghan[13]; concentrations are reported as micrograms of lidocaine base per milliliter of plasma ($\mu g \cdot ml^{-1}$) or per gram of tissue ($\mu g \cdot g^{-1}$).

The data were statistically analyzed by using chi-square, Student's *t*, and least-squares linear regression techniques. Data are expressed as mean values ± 1 standard deviation (SD) or standard error of the mean (SE) as indicated. A probability of chance occurrence less than 5% ($P < 0.05$) was considered significant.

Results

Among the 47 dogs studied, ventricular dysrhythmias occurred after LAD occlusion in 40, as manifested by ventricular premature contractions in 31 dogs and by ventricular tachycardia in nine. For all 40 dogs that had dysrhythmias after LAD occlusion, the interval from LAD occlusion to the onset of the arrhythmia averaged 155 s and that from the onset of arrhythmia to lidocaine administration, 22 s. Among the 40 dogs with dysrhythmias, each of the 14 dogs that received lidocaine doses of 120 mg (5.7 ± 0.7 $mg \cdot kg^{-1}$, SD, n = 5), 80 mg (3.3 $mg \cdot kg^{-1}$, n = 2), or 40 mg (1.7 ± 0.1 $mg \cdot kg^{-1}$, SD, n = 7) had a positive antidysrhythmic effect as defined, and each had $[L]_I$ greater than 1.0 $\mu g \cdot g^{-1}$.

The 26 dogs that had ventricular dysrhythmias after LAD occlusion and that received 20 mg (0.99 ± 0.13 $mg \cdot kg^{-1}$, SD) of lidocaine had an approximately equal distribution of positive and negative rhythm responses (54%, n = 14, had an antidysrhythmic effect and 46%, n = 12, did not). Therefore, the 20-mg lidocaine dose

approximated an ED_{50} for the antidysrhythmic response in this model, and the subgroup of dogs that received this dose of lidocaine forms the data base for subsequent analyses. Among the dogs that received 20 mg of lidocaine, the incidence of frequent ventricular premature contractions and ventricular tachycardia before lidocaine injection was the same in both response groups. The time from the onset of the dysrhythmia to the administration of lidocaine (20 mg) did not differ when dogs with an antidysrhythmic effect and those without were compared (18.8 ± 3.9 *vs.* 16.1 ± 4.6 s, respectively, NS). Also the $mg \cdot kg^{-1}$ lidocaine dose with the 20 mg injection did not differ significantly when the two response groups were compared (1.04 ± 0.09 *vs.* 0.94 ± 0.14 $mg \cdot kg^{-1}$, respectively, NS). The time from lidocaine (20 mg) injection to blood and tissue sampling was a mean of 112 s for the dogs that had an antidysrhythmic effect (range 32–444 s) compared with a mean of 111 s for those that did not (range 28–442 s).

Lidocaine concentration achieved by the 20-mg dose in arterial plasma ($[L]_A$), venous plasma ($[L]_V$), and in normal and ischemic myocardium is shown in table 1. While $[L]_V$, $[L]_A$, and $[L]_N$ did not differ when the dogs with an antidysrhythmic effect were compared with those without that effect, the dogs with an antidysrhythmic effect had an $[L]_I$ that was significantly higher than the nonresponding dogs had (1.14 ± 0.12 *vs.* 0.76 ± 0.04 $\mu g \cdot g^{-1}$, $P < 0.025$, table 1). Lidocaine produced an antidysrhythmic effect in nine of 10 dogs that had an $[L]_I$ greater than or equal to 1.0 $\mu g \cdot g^{-1}$, while ventricular dysrhythmias persisted in 11 of 16 in which $[L]_I$ was less than 1.0 $\mu g \cdot g^{-1}$ (chi-square = 8.55, $P < 0.005$).

Among the 26 dogs that received 20 mg of lidocaine after the onset of dysrhythmia, the systemic hemodynamic response to lidocaine consisted of a small but statistically significant decline in mean arterial pressure (100 ± 4.5 to 90 ± 2.8 mmHg, $P < 0.05$) and no change in heart rate; this response occurred 23 ± 3 s (SD) after injection. Neither the change in heart rate nor the change in arterial pressure differed when the two response groups were compared. In the 14 dogs that had an antidysrhythmic response to lidocaine, the time from lidocaine injection to decrease in arterial pressure and from lidocaine injection to rhythm effect correlated closely (fig. 1). The $RMBF_I$ was 9.8 ± 1.5% of $RMBF_N$ in the dogs that had an antidysrhythmic effect and 6.9 ± 1.3% of $RMBF_N$ in those that did not ($P < 0.05$). While $[L]_I$ correlated closely with $RMBF_I$ (fig. 2), $[L]_N$ and $RMBF_N$ did not correlate closely: $[L]_N = -0.01$ ($RMBF_N$) + 6.21, $r = 0.06$.

TABLE 1. Lidocaine Concentrations after an Intravenous Bolus of 20 mg

Lidocaine Concentration	Antidysrhythmic Effect (n = 14)	No Antidysrhythmic Effect (n = 12)
Arterial plasma ($mg \cdot ml^{-1}$)	9.20 ± 2.2	7.70 ± 1.80
Venous plasma ($mg \cdot ml^{-1}$)	2.00 ± 0.4	1.90 ± 0.30
Normal myocardium ($mg \cdot ml^{-1}$)	5.90 ± 0.5	5.30 ± 0.60
Ischemic myocardium ($mg \cdot ml^{-1}$)	1.14 ± 0.12	0.76 ± 0.04*

Values are mean ± SE.
* Compared with the antidisrhythmic effect, $P < 0.025$.

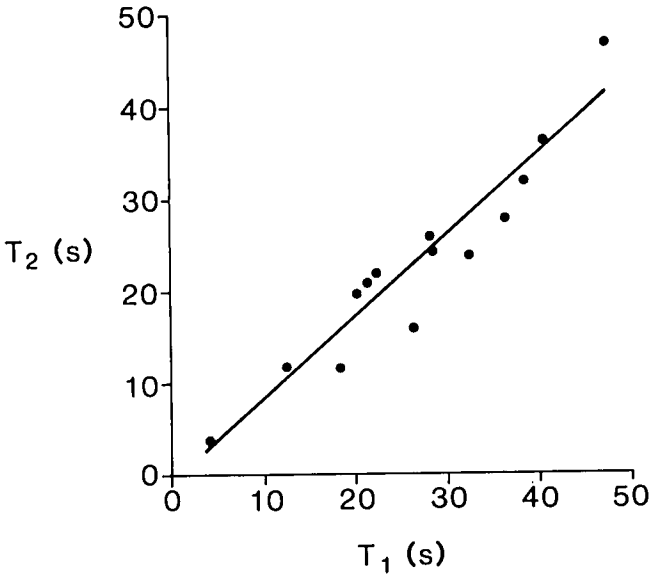

FIG. 1. Among the 14 dogs that had an antidysrhythmic response following a 20-mg intravenous lidocaine dose, the relationship between the time interval from lidocaine administration to a decrease in mean arterial pressure (T_1) and the time interval from lidocaine administration to the antiarrhythmic effect (T_2) is given by the regression equation, $T_1 = 0.89\ (T_2) \pm 0.15$, $r = 0.94$.

Analysis of the time course of myocardial lidocaine concentration shows a marked difference between the normal and the ischemic myocardium. $[L]_N$ correlated closely with the time interval from lidocaine injection to tissue sampling, $\log [L]_N = -0.0014$ (time) + 0.86, $r = 0.82$. In contrast, $[L]_I$ did not correlate with the time interval from lidocaine injection to tissue sampling, $\log [L]_{IM} = -0.0002$ (time) + 0.97, $r = 0.07$. However, both $[L]_N$ and $[L]_I$ correlated strongly to the dose of lidocaine (fig. 3).

Ischemic myocardial lidocaine concentration and $RMBF_I$ were analyzed as a percentage of the normal myocardial values for the dogs that received the 20-mg lidocaine dose; $[L]_I$ (per cent of normal) was greater than $RMBF_I$ (per cent of normal), 28.1 ± 4.4% *versus* 11.0 ± 1.7%, respectively (fig. 4) ($P < 0.001$). Ischemic myocardium with $RMBF_I$ 10–50% of normal (mean value 19 ± 1.8%, SE) had an $[L]_I$ of 41.4 ± 6.6% of normal and severely ischemic myocardium, with $RMBF_I$

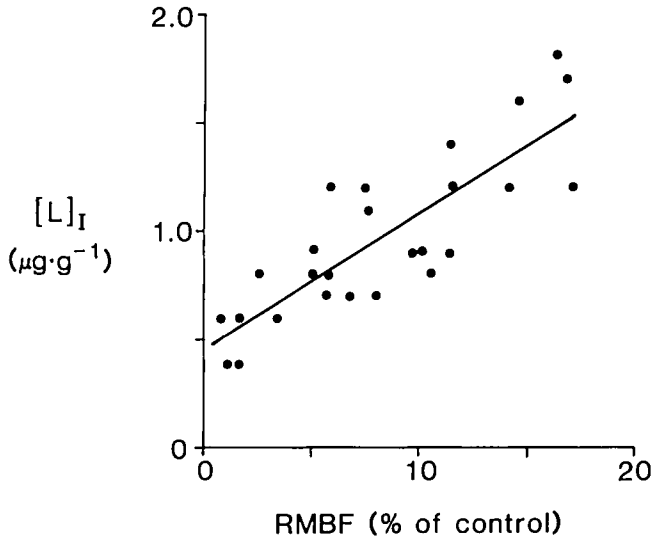

FIG. 2. The relationship between lidocaine concentration in ischemic myocardium ($[L]_I$) and regional myocardial blood flow in ischemic myocardium (RMBF), expressed as a per cent of RMBF to normal myocardium for the 26 dogs that were treated with 20 mg of lidocaine, is given by the regression equation, $[L]_I = 0.07$ (%RMBF) $= +0.41$, $r = 0.85$.

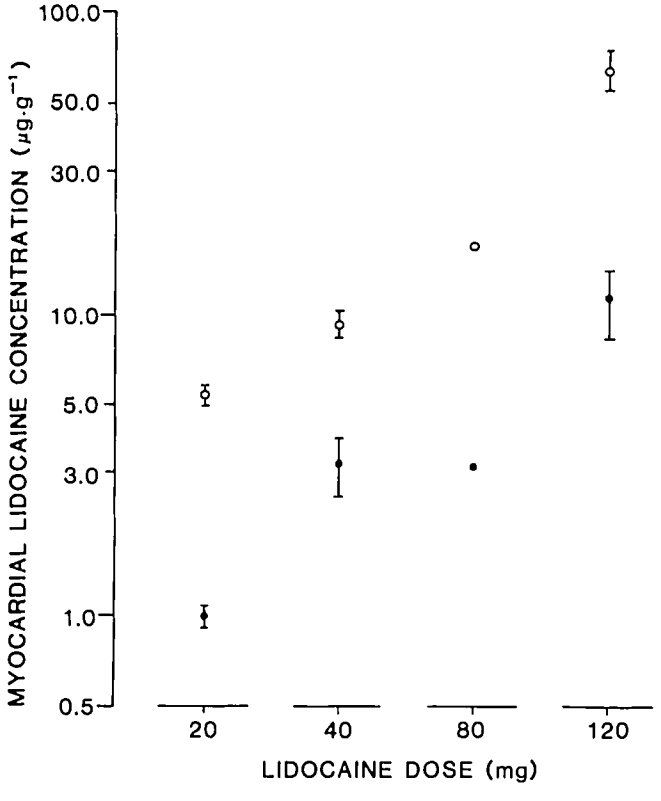

FIG. 3. The relationship between the dose of lidocaine and myocardial lidocaine concentration is shown with open circles to indicate mean values for each lidocaine dose in normal myocardium and closed circles to indicate corresponding values for ischemic myocardium. Error brackets are not displayed for the myocardial concentrations obtained after the 80-mg dose of lidocaine, as these values are simply the average of two data points.

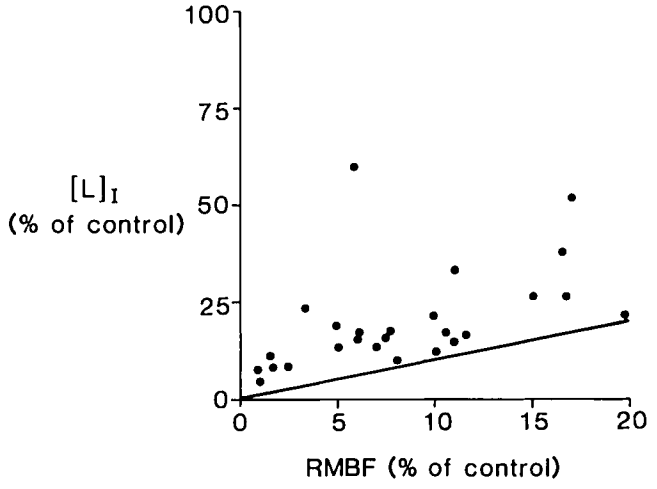

FIG. 4. The relationship between lidocaine concentration and regional myocardial blood flow (RMBF) in ischemic myocardium is shown with both variables expressed as a per cent of the respective control value from normal myocardium. Note the distribution of data points above the identity line.

less than 10% of normal (mean value 5.3 ± 0.7%, SE) had an $[L]_I$ of 15.2 ± 2.0% of normal.

Discussion

The principal finding of this study is that the antidysrhythmic effect of lidocaine depends on the concentration of lidocaine achieved within the ischemic myocardium following a single intravenous bolus dose of lidocaine. This result is consistent with previous studies demonstrating that ectopic foci in the ischemic myocardium produce the ventricular ectopy of the acute phase of myocardial infarction.[4,5] In the present investigation, various lidocaine dosages were used to determine a single lidocaine dose that would produce an antidysrhythmic effect in approximately 50% of experimental animals in which ischemic ventricular dysrhythmias had been produced by high ligation of the LAD. Using this dosage (which approximates an ED_{50} in the present model), the pharmacokinetic parameters of lidocaine concentration within both normal and ischemic myocardium were examined. The data show that the antidysrhythmic effect of lidocaine is dependent upon the concentration present in ischemic myocardium; however, no such dependence was seen for arterial, venous, or normal myocardial lidocaine concentration. Furthermore, an $[L]_I$ of 1 $\mu g \cdot g^{-1}$ was the apparent threshold for this antidysrhythmic effect.

Zito *et al.*[14] have shown that regional myocardial lidocaine kinetics during an acute infarction differ from those seen 24 h after infarction. During the acute phase of infarction, using a continuous infusion of lidocaine, these authors demonstrated higher lidocaine concentra-

tion in ischemic regions than in normally perfused regions. This effect was not seen 24 h after infarction. In an earlier study,[15] this same group reported that tissue lidocaine concentration was reduced less in ischemic than in normal myocardium 5 min after bolus injection. They concluded that, after the initial distribution of a bolus injection, washout—a function of regional blood flow—was the dominant factor in regional myocardial lidocaine concentration.

Wenger *et al.*[10] demonstrated a difference between normal and ischemic myocardium with regard to the regional concentration of procainamide obtained after a single intravenous bolus. Procainamide concentration was shown to decline more rapidly in normal myocardium than in ischemic areas, and this observation led to the conclusion that the ischemic myocardium represents a tissue compartment whose pharmacokinetic distance from the central compartment is a function of the severity of ischemia. Using a constant infusion technique for procainamide,[16] this same group demonstrated a reduction in ischemic myocardial procainamide concentration only after RMBF declined to 31–40% of control; even with RMBF less than or equal to 10% of control, ischemic myocardial procainamide was still 42% of control. Again, the authors concluded that there is substantial concentration of procainamide in markedly ischemic myocardium.

The results of the present investigation are consistent with these studies. We have shown that myocardial [L] and RMBF in ischemic tissue strongly correlate, however, proportionally, [L] is consistently higher than RMBF in ischemic myocardium (fig. 4). This relationship was not seen for normal myocardium, perhaps because the high RMBF produced a rapid washout of lidocaine from the normal myocardium as noted by Zito *et al.*[15] This disproportionate amount of lidocaine relative to RMBF indicates a difference between lidocaine kinetics in ischemic myocardium and normal myocardium. This difference may be explained by an increased avidity of the ischemic myocardium for lidocaine, a slower "washout" of the drug because of diminished RMBF, or both. An increased avidity of ischemic myocardium for lidocaine could result from the influence that *p*H is known to have on the distribution of local anesthetic agents across biologic membranes.[17] Since the pK_a of lidocaine approximates 7.9,[18] a relatively small decrease in *p*H within the physiologic range will have a large effect on the relative concentrations of uncharged lidocaine base and its ionized form. Previous studies have shown that a reduction in myocardial cellular *p*H is associated with a reduction in RMBF.[19,20] Such a reduction in intracellular *p*H would increase the proportion of the cationic, membrane-impermeable form of lidocaine within the ischemic cells and could account for the retention of a larger amount of lidocaine in ischemic myocardium. Similar ion-trapping mechanisms have been postulated for the increased fetal–maternal lidocaine ratio observed during fetal acidosis[21] and for the increased excretion of lidocaine produced by urinary acidification.[22] However, Yakaitis *et al.* could not show an influence of acid–base imbalance on the cardiovascular response to lidocaine.[23]

The avidity of ischemic myocardium for lidocaine also could be increased by enhanced binding of the drug to cellular membranes. The lipid membranes of myocardial cells are altered markedly by ischemia.[24] Permeability and binding properties of such damaged membranes for lidocaine may differ from those in the normal state. Alternatively, decreased blood flow could account for a slower redistribution of the drug from ischemic than from normal myocardium and, thus, a greater proportion of a lidocaine bolus being retained by ischemic tissue than by normal tissue. All of these proposed mechanisms would be influenced by the magnitude of the ischemic zone. However, infarct size was not measured in these acute studies.

In conclusion, the concentration of lidocaine in the ischemic myocardium (but not that found in arterial plasma, venous plasma, or normal myocardium) was related significantly to the antiarrhythmic response after a single intravenous bolus of lidocaine. An ischemic myocardial lidocaine concentration of 1 $\mu g \cdot g^{-1}$ was determined to be the apparent threshold of this antiarrhythmic effect. The close relationship between ischemic myocardial lidocaine concentration and ischemic RMBF may explain, in part, the variable effect of a given lidocaine dose on ventricular dysrhythmias produced by ischemia in the clinical setting, because blood flow to the ischemic area may vary substantially. The lack of correlation between $[L]_V$ or $[L]_A$ and rhythm response in the present investigation is likely to be due to the non-steady-state conditions obtained by using a single iv bolus and should not be interpreted as indicating a lack of utility in measuring $[L]_V$ to guide long-term lidocaine treatment by continuous infusion. Additionally, the regional pharmacokinetic parameters of lidocaine within the ischemic myocardium differ from those within the normal myocardium, an effect perhaps due to an increased avidity of ischemic myocardium for lidocaine, secondary to either ion-trapping produced by the acidic nature of the ischemic myocardium or to alteration of lipid membranes, or perhaps due to a diminished rate of lidocaine washout from the ischemic myocardium due to reduced blood flow.

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