Failure of Antiarrhythmic Drugs to Prevent Experimental Reperfusion Ventricular Fibrillation

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SUMMARY Ninety-nine adult mongrel dogs underwent acute ligation of the proximal left anterior descending coronary artery. Thirty minutes later, the occlusion was released to evaluate the effectiveness of five antiarrhythmic protocols in eliminating reperfusion ventricular fibrillation. The five protocols included: protocol 1 — i.v. lidocaine, preligation and prerelease (n = 19); protocol 2 — i.v. lidocaine, prereperfusion only (n = 22); protocol 3 — chronic, oral, daily amiodarone for 2 weeks preligation (n = 19); protocol 4 — i.v. procainamide, preligation and prereperfusion (n = 21); and protocol 5 — i.v. verapamil, prereperfusion (n = 18). Each regimen was evaluated with respect to the incidence of reperfusion ventricular fibrillation in dogs that survived to reperfusion, and the results were compared to 77 control dogs that underwent identical coronary artery occlusion and release procedures without drug therapy. The incidence of reperfusion ventricular fibrillation was as follows: protocol 1 — seven of 15 dogs (47%); protocol 2 — six of 18 (33%); protocol 3 — 11 of 16 dogs (69%); protocol 4 — eight of 17 dogs (47%); and protocol 5 — 10 of 17 dogs (59%), compared with 36 of 60 (60%) in control dogs.

Using chi-square analysis, protocol 2 was beneficial (p < 0.05). The dogs were then stratified into high- and low-risk subgroups based on the arrhythmic events of the antecedent coronary artery ligation period, and predictive risk indexes for the occurrence of reperfusion ventricular fibrillation were developed. The Mantel-Haenszel method of statistical analysis revealed that none of these protocols resulted in a statistically significant reduction in the incidence of reperfusion ventricular fibrillation. Thus, use of these predictive indexes plus appropriate statistical methods has revealed, unexpectedly, limitations in the efficacy of a spectrum of antiarrhythmic agents in preventing reperfusion ventricular fibrillation.

CANINE coronary artery occlusion and reperfusion models have been studied extensively as a means for understanding the life-threatening ventricular arrhythmias that occur after myocardial ischemia and infarction. However, as useful as these canine models have been in revealing electrophysiologic mechanisms,1-99 their use as models for evaluating antiarrhythmic drug interventions has led to equivocal and contradictory results.17-20 Other studies, using either coronary artery ligation or reperfusion models, have also suggested that a large and variable number of animals do not develop ventricular fibrillation, even without prior antiarrhythmic therapy (approximately 60% and 30%, respectively).9-20

Previous studies in this laboratory, however, indicate that the risk for developing ventricular fibrillation on reperfusion might be predicted for individual animals based on the incidence, time course and severity of arrhythmias occurring during the antecedent period of acute coronary artery ligation.96, 97 This was predicated on the observation that different animals subjected to acute one-stage ligation of the proximal left anterior descending coronary artery developed either immediate (occurring 2–12 minutes
after ligation), delayed (occurring 14–30 minutes after ligation), both types or no ventricular arrhythmias at all;33, 35 and that the risk for ventricular fibrillation during the subsequent period of coronary artery reperfusion correlated closely with the occurrence of these ligation arrhythmias.30, 31

In the present study we evaluated the effectiveness of lidocaine, procainamide, amiodarone and verapamil in preventing ventricular fibrillation after acute coronary artery reperfusion. For this purpose, the results of various treatment protocols were compared, adjusting for differences in the arrhythmic events that occurred during earlier periods of coronary artery ligation. Using these methods, we have avoided some of the limitations imposed by the inconsistencies reported in previous studies.

Methods

Ninety-nine dogs were studied on various drug regimens. Adult 15–30-kg mongrel dogs were anesthetized with i.v. pentobarbital sodium, 30 mg/kg, and immediately intubated. Room air ventilation was maintained with a Harvard respirator and body temperature was maintained with a thermal blanket. A #8F NIH catheter was introduced into the ascending aorta via the femoral artery to monitor the aortic pressure throughout each experiment. The chest was opened through the fifth left intercostal space, the pericardium opened and the heart suspended in a pericardial cradle. The left anterior descending coronary artery was dissected free and a snare was positioned within 2 cm of its origin and proximal to all diagonal branches. Two surface ECG leads were monitored continuously on a C-59 Tektronix storage oscilloscope and recorded on a Model #4578A Hewlett-Packard eight-channel photographic recorder. In all dogs the coronary artery was ligated in one stage, the occlusion maintained for 30 minutes and then acutely released. At the time of release, the vessel was gently kneaded to ensure rapid return of maximum pulsatile blood flow. A 30-minute period of coronary artery ligation was chosen to incorporate both the immediate and delayed ligation ventricular arrhythmias and because previous studies showed that the incidence of ventricular fibrillation after reperfusion was highest after a ligation period of this duration.30–33

Whenever ventricular fibrillation occurred, dogs received DC shocks of 10 watt-sec and if fibrillation persisted, a second shock of 40 watt-sec was delivered to the heart. Dogs that were successfully resuscitated after no more than the two attempts described were considered appropriate for reperfusion.

The dogs were divided into five subgroups. Drug regimens were chosen to facilitate both optimal plasma and tissue levels in both normal and ischemic myocardium at the time of reperfusion, 30 minutes after ligation.24–42

Drug Protocol 1, Lidocaine

Nineteen dogs received 1 mg/kg of lidocaine in a bolus injection 3 minutes before ligation of the coronary artery; a 0.07-mg/kg.min infusion was started and continued for the remainder of the experiment. At 27 minutes after ligation and 3 minutes before reperfusion, an additional 1-mg/kg i.v. bolus of lidocaine was given to the 15 surviving dogs.

Drug Protocol 2, Lidocaine

Twenty-two dogs that underwent coronary artery ligation were included in this group, but only 18 survived to the reperfusion phase. A bolus of 1.0 mg/kg of lidocaine was given 3 minutes before the release of the occlusion, followed by a 0.07-mg/kg.min i.v. infusion to the 18 dogs that survived coronary artery ligation. This protocol was included so we could exclude any effects of lidocaine on the occurrence of reperfusion ventricular arrhythmias caused by the effects of lidocaine during the period of coronary artery ligation (drug protocol 1).

Drug Protocol 3, Amiodarone

Nineteen dogs received 10 mg/kg of amiodarone orally every day for 14 days before acute occlusion of the left anterior descending coronary artery.

Drug Protocol 4, Procainamide

Twenty-one dogs received an i.v. bolus of 20 mg/kg of procainamide 30 minutes before coronary artery ligation, over 2 minutes, followed by a 0.1-mg/kg.min infusion that was continued throughout ligation and reperfusion. Twenty minutes after ligation and 10 minutes before reperfusion, the 17 surviving dogs received a second bolus of 10 mg/kg of procainamide.

Drug Protocol 5, Verapamil

Eighteen dogs were included in the verapamil protocol and 17 survived to reperfusion. Seven minutes before reperfusion, each of these animals received 0.2 mg/kg of i.v. verapamil. Because previously published drug protocols were adhered to, blood levels were not monitored on the various treatment protocols.

Control Dogs

Seventy-seven control dogs were treated identically except that no antiarrhythmic agents were administered either before coronary artery ligation, during ligation or during coronary artery reperfusion. These dogs were studied as a consecutive series to detail electrophysiologic mechanisms of coronary artery ligation and reperfusion ventricular arrhythmias, and were in every other way comparable to the study dogs.

Definitions

The following ventricular arrhythmias were tabulated: ventricular fibrillation and ventricular arrhythmias, but no ventricular fibrillation. This included dogs with at least five ventricular ectopic beats per minute or ventricular tachycardia (≥ triplets.)
Immediate (IVA) and delayed (DVA) ventricular arrhythmias were defined as previously reported. The IVAs were those that occurred 2-12 minutes after acute coronary artery ligation and peaked at 5 minutes, and the DVAs were defined as those that occurred 14-30 minutes after coronary artery ligation and peaked at 18 minutes. Only reperfusion ventricular arrhythmias that occurred within 15 minutes of release of occlusion were included in this analysis.

Statistical Methods

The data were initially subjected to a conventional chi-square analysis. The Mantel-Haenszel method of statistical analysis was then applied to take into account the observation that different subgroups were at different relative risks for the occurrence of reperfusion ventricular fibrillation based on the arrhythmic events of the antecedent period of coronary artery ligation; and that various protocols included different proportions of dogs in these subgroups. The Mantel-Haenszel method of data analysis is appropriate for combining information from several subgroups to test for an overall association. This method assigns greater weight to subgroups with more subjects and uses an unbiased estimate of the variance of the association in each subgroup, as well as a correction for finite population size. However, this method also has the potential limitation of obscuring the effect of an intervention on any one relatively small subgroup within a larger population.

Using these statistical methods, we could take into account possible sampling errors in the proportions of dogs in the control and treated groups with ventricular fibrillation after reperfusion. Both the Mantel-Haenszel and chi-square analyses are large-sample statistical methods for which the test statistic is approximately distributed as the chi-square random variable for large sample sizes. The p value associated with the chi-square method was calculated using a series approximation to the cumulative distribution function of a chi-square random variable (Stat Pak I, Hewlett-Packard, 1976). The p values reported in the text for different treatment protocols are those derived using the Mantel-Haenszel analysis unless otherwise noted.

Results

Control Group

Seventy-seven consecutive dogs were studied in the control group (fig. 1). Sixteen dogs (21%) had no ventricular arrhythmias during the coronary artery ligation period and 34 (44%) had ventricular fibrillation during ligation. Seventeen of the 34 dogs with ventricular fibrillation survived to reperfusion after resuscitation. Sixty dogs survived to reperfusion and 36 (60%) developed ventricular fibrillation; of the 44 dogs with ligation ventricular arrhythmias, 36 (82%) had ventricular fibrillation on reperfusion. No dogs in the group free of coronary artery ligation arrhythmias suffered ventricular fibrillation on reperfusion, whereas all 17 dogs (100%; six DVA only, 11 IVA + DVA) resuscitated from ventricular fibrillation during antecedent ligation again had ventricular fibrillation on reperfusion. Dogs with only IVA, only

**Figure 1.** Results of acute ligation of the proximal left anterior descending coronary artery and reperfusion 30 minutes later in 77 control dogs. Sixty dogs were available for reperfusion, including 44 with ligation ventricular arrhythmias. CAL = coronary artery ligation; DVA = delayed ventricular arrhythmias; IVA = immediate ventricular arrhythmias; R = reperfusion; VA = ventricular arrhythmias; VF = ventricular fibrillation.
DVA, or both were at progressively increasing risk, respectively, for the occurrence of reperfusion-related ventricular fibrillation. Therefore, using the 77 control dogs, we could develop a predictive index for the occurrence of reperfusion ventricular fibrillation for any dog based on the events of the immediately preceding period of acute coronary artery ligation (fig. 1, table 1). For example, dogs with both IVA and DVA but not ventricular fibrillation were still at considerable risk (86%) for developing ventricular fibrillation during reperfusion.

Drug Protocol 1

Nineteen dogs were pretreated with lidocaine, as detailed in the Methods (fig. 2). Three (16%) had no ventricular arrhythmias during coronary artery ligation, four (21%) died of refractory ventricular fibrillation during the period of IVA, and eight of 19 dogs (42%) developed ventricular fibrillation during coronary ligation. None of these results differed from the control group (i.e., treatment with lidocaine pre-ligation in this manner did not affect the appearance of these ligation ventricular arrhythmias). Twelve dogs with ligation ventricular arrhythmias survived to reperfusion, including four dogs with ligation-related

| Table 1. Reperfusion Ventricular Fibrillation Predictive Indexes* |
|---------------------------------|---|---|---|
| Dogs with: | n | R-VF | Risk |
| No CAL VA or VF | 16 | 0 | 0% | 0.00 |
| IVA - VA | 5 | 2 | 40% | 0.40 |
| - VF | 0 | - | - | - |
| DVA - VA | 8 | 5 | 63% | 0.63 |
| - VF | 6 | 6 | 100% | 1.00 |
| IVA + DVA | - VA | 14 | 12 | 86% | 0.86 |
| - VF | 11 | 11 | 100% | 1.00 |
| CAL - VF | 17 | 17 | 100% | 1.00 |

*Based on dogs that survived 30 minutes of coronary artery ligation.
†No dogs in this category.

Abbreviations: CAL = coronary artery ligation; DVA = delayed ventricular arrhythmias; IVA = immediate ventricular arrhythmias; n = number of dogs at risk (i.e., surviving 30 minutes of CAL and subjected to reperfusion); R = reperfusion; VA = ventricular arrhythmias; VF = ventricular fibrillation.

**Figure 2.** Results of acute ligation and reperfusion of the proximal left anterior descending coronary artery in dogs treated with lidocaine, beginning with an i.v. bolus before ligation, a constant infusion continuing through ligation and reperfusion, and an additional bolus just before reperfusion. Fifteen dogs were available for reperfusion, including 12 with ligation ventricular arrhythmias. CAL = coronary artery ligation; DVA = delayed ventricular arrhythmias; IVA = immediate ventricular arrhythmias; R = reperfusion; VA = ventricular arrhythmias; VF = ventricular fibrillation.

**TABLE 1. Reperfusion Ventricular Fibrillation Predictive Indexes***

<table>
<thead>
<tr>
<th>Dogs with:</th>
<th>n</th>
<th>R-VF</th>
<th>Risk</th>
<th>Predictive index</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CAL VA or VF</td>
<td>16</td>
<td>0</td>
<td>0%</td>
<td>0.00</td>
</tr>
<tr>
<td>IVA - VA</td>
<td>5</td>
<td>2</td>
<td>40%</td>
<td>0.40</td>
</tr>
<tr>
<td>- VF</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DVA - VA</td>
<td>8</td>
<td>5</td>
<td>63%</td>
<td>0.63</td>
</tr>
<tr>
<td>- VF</td>
<td>6</td>
<td>6</td>
<td>100%</td>
<td>1.00</td>
</tr>
<tr>
<td>IVA + DVA</td>
<td>- VA</td>
<td>14</td>
<td>12</td>
<td>86%</td>
</tr>
<tr>
<td>- VF</td>
<td>11</td>
<td>11</td>
<td>100%</td>
<td>1.00</td>
</tr>
<tr>
<td>CAL - VF</td>
<td>17</td>
<td>17</td>
<td>100%</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Based on dogs that survived 30 minutes of coronary artery ligation.
†No dogs in this category.

Abbreviations: CAL = coronary artery ligation; DVA = delayed ventricular arrhythmias; IVA = immediate ventricular arrhythmias; n = number of dogs at risk (i.e., surviving 30 minutes of CAL and subjected to reperfusion); R = reperfusion; VA = ventricular arrhythmias; VF = ventricular fibrillation.
ventricular fibrillation. Based on the predictive indexes derived from the 77 control dogs (fig. 1, table 1), 9.7 dogs (81%) would have been expected to develop ventricular fibrillation on reperfusion, but only seven of 12 (58%) animals did. This difference in the occurrence of ventricular fibrillation was not statistically significant ($p > 0.10$).

**Drug Protocol 2**

Twenty-two dogs underwent acute coronary artery ligation and were treated with lidocaine beginning 3 minutes before reperfusion, but not before ligation (fig. 3). Dogs treated in this manner were comparable to the controls and to the dogs treated with lidocaine before both ligation and reperfusion (i.e., drug protocol 1) with respect to the number (i.e., proportion) of dogs free of ventricular arrhythmias during the coronary artery ligation period, the number of dogs that died with ventricular fibrillation during the period of IVA, and in the number with ventricular fibrillation during the period of ligation ($p > 0.10$). Eleven dogs with ventricular arrhythmias during ligation survived to reperfusion, including three dogs with ligation ventricular fibrillation. We predicted that 9.0 (82%) of these 11 dogs would have incurred ventricular fibrillation with reperfusion, but only six (54.5%) did. However, this difference was not statistically significant ($p > 0.10$).

**Drug Protocol 3**

Nineteen dogs were pretreated with amiodarone before coronary artery ligation, as described in the Methods (fig. 4). Compared with controls, there was no difference during the coronary artery ligation period in the number of dogs that died with refractory ventricular fibrillation during IVA or in the number of dogs with ventricular fibrillation during coronary artery ligation ($p > 0.10$). Thus, 13 dogs were subjected to coronary artery reperfusion, including five dogs resuscitated from ventricular fibrillation; these dogs were no different from the controls with respect to the incidence of arrhythmias during ligation. We predicted that 10.5 of these 13 dogs (81%) would have succumbed to reperfusion ventricular fibrillation, and 11 (85%) did so. This difference was not statistically significant ($p > 0.10$).

**Drug Protocol 4**

Twenty-one dogs were pretreated with procainamide beginning 30 minutes before ligation (fig. 5). As detailed in the Methods, dogs were then maintained on a constant infusion in addition to receiving a second bolus before reperfusion. Dogs pretreated in this manner did not differ from controls with respect to the number of dogs free of ventricular arrhythmias during the coronary artery ligation

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**LIDOCAINE : pre-reperfusion**

<table>
<thead>
<tr>
<th>N = 15 (CAL VA)</th>
<th>Died</th>
<th>IVA / VF</th>
<th>VA</th>
<th>VF</th>
<th>IVA only</th>
<th>DVA only</th>
<th>IVA + DVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>1 (5%)</td>
<td>1</td>
<td>0</td>
<td>1 (5%)</td>
<td>4 (8%)</td>
<td>6 (27%)</td>
</tr>
</tbody>
</table>

**Observed R-VF**: 6 (total)

**Predicted R-VF**: 9.0 (total)

![Figure 3](image)

*Results of acute ligation and reperfusion of the proximal left anterior descending coronary artery in dogs treated with i.v. lidocaine beginning with a bolus 3 minutes before reperfusion and continuing with a constant infusion through reperfusion. Eighteen dogs were available for reperfusion, including 11 with ligation ventricular arrhythmias. CAL = coronary artery ligation; DVA = delayed ventricular arrhythmias; IVA = immediate ventricular arrhythmias; R = reperfusion; VA = ventricular arrhythmias; VF = ventricular fibrillation.*
RESULTS OF ACUTE LIGATION AND REPERFUSION OF THE PROXIMAL LEFT ANTERIOR DESCENDING CORONARY ARTERY IN 19 DOGS THAT RECEIVED CHRONIC ORAL DAILY AMIODARONE FOR THE 2 WEEKS BEFORE CORONARY ARTERY LIGATION. SIXTEEN DOGS WERE AVAILABLE FOR REPERFUSION, INCLUDING 13 WITH LIGATION VENTRICULAR ARRHYTHMIAS. CAL = CORONARY ARTERY LIGATION; DVA = DELAYED VENTRICULAR ARRHYTHMIAS; IVA = IMMEDIATE VENTRICULAR ARRHYTHMIAS; R = REPERFUSION; VA = VENTRICULAR ARRHYTHMIAS; VF = VENTRICULAR FIBRILLATION.

RESULTS OF ACUTE LIGATION AND REPERFUSION OF THE PROXIMAL LEFT ANTERIOR DESCENDING CORONARY ARTERY IN 21 DOGS TREATED WITH PROCAINAMIDE, BEGINNING WITH AN I.V. LOADING DOSE BEFORE LIGATION, A CONSTANT INFUSION CONTINUING THROUGH LIGATION AND REPERFUSION, AND WITH AN ADDITIONAL I.V. BOLUS BEFORE REPERFUSION. SEVENTEEN DOGS WERE AVAILABLE FOR REPERFUSION, INCLUDING 11 WITH LIGATION VENTRICULAR ARRHYTHMIAS. CAL = CORONARY ARTERY LIGATION; DVA = DELAYED VENTRICULAR ARRHYTHMIAS; IVA = IMMEDIATE VENTRICULAR ARRHYTHMIAS; R = REPERFUSION; VA = VENTRICULAR ARRHYTHMIAS; VF = VENTRICULAR FIBRILLATION.
period, the number of dogs that died with refractory ventricular fibrillation during the period of IVA or in the number with ventricular fibrillation during coronary artery ligation \((p > 0.10)\). Eleven dogs with ventricular arrhythmias during the antecedent period of coronary artery ligation survived to reperfusion, including four dogs resuscitated from ligation ventricular fibrillation. We predicted that 9.6 dogs (87%) would have developed ventricular fibrillation on reperfusion, and eight dogs (73%) did so. This difference was not statistically significant \((p > 0.10)\).

**Drug Protocol 5**

Eighteen dogs underwent coronary artery ligation and subsequent i.v. verapamil treatment before reperfusion, as detailed in the Methods. Their course is detailed in figure 6. We predicted that 8.9 of the 11 dogs (81%) with ligation ventricular arrhythmias surviving to reperfusion would have had ventricular fibrillation with reperfusion, and 10 (91%) did so. This difference was not statistically significant \((p > 0.10)\).

**Summary Data**

Fifty-eight of the dogs (58%) in the different drug-treated groups survived to reperfusion. Using the predictive indexes derived from the control dogs, we expected that 47.7 of these 58 dogs (82%) surviving to reperfusion in the drug-treated groups would have incurred reperfusion ventricular fibrillation, and 42 (72%) did. This difference was not statistically significant \((p > 0.10)\).

![Diagram](https://via.placeholder.com/150)

**Figure 6.** Results in dogs treated with a single i.v. loading dose of verapamil administered before reperfusion. Seventeen dogs were available for reperfusion, including 11 with ligation ventricular arrhythmias. **CAL** = coronary artery ligation; **DVA** = delayed ventricular arrhythmias; **IVA** = immediate ventricular arrhythmias; **R** = reperfusion; **VA** = ventricular arrhythmias; **VF** = ventricular fibrillation.
controls) in this study, consideration of the Bonferroni adjustment is appropriate. Thus, an approximately 0.05/5 = 0.01 level of significance would be required to demonstrate, conservatively, a reduction in the incidence of reperfusion ventricular fibrillation attributable to a drug protocol.

Discussion

The purpose of the present study was to evaluate the effectiveness of a spectrum of antiarrhythmic agents with diverse electrophysiologic properties in preventing reperfusion-related ventricular fibrillation. In this malignant model, we have focused on the lethal end point of ventricular fibrillation, rather than electrophysiologic markers such as ventricular ectopy or fractionation of local electrograms.10-12

The design of this study allowed us to evaluate these agents with respect to their roles in both the primary (prophylactic, before an ischemic event) and secondary (postischemic, before reperfusion) prevention of ventricular fibrillation.

Primary Antiarrhythmic Prophylaxis

Initiation of antiarrhythmic therapy with either lidocaine, amiodarone, or procainamide before ligation did not eliminate, and did not even reduce significantly \( (p > 0.10) \) the occurrence of ventricular fibrillation resulting from reperfusion 30 minutes after acute coronary artery ligation. Furthermore, these same agents were also ineffective in reducing the incidence of ventricular fibrillation and ventricular arrhythmias during the antecedent 30-minute periods of coronary artery ligation. Initiation of antiarrhythmic therapy before initial ligation in this study was done in accord with previously reported pharmacokinetic data to ensure that adequate drug concentrations were not only circulating, but were also present in both normal and presumably ischemic myocardium.34, 41

These findings have two implications. First, chronic and prophylactic primary (i.e., before any ischemic event) administration of lidocaine, amiodarone or procainamide would not be expected to be optimally protective against subsequent reperfusion-related ventricular fibrillation.

Second, chronic administration of amiodarone would not be adequate prophylaxis against ventricular fibrillation occurring as a result of either acute coronary artery ligation or subsequent reperfusion. In addition, the present data suggest that lidocaine and procainamide are also not protective against ligation ventricular arrhythmias. However, these results do not preclude the possibility that additional benefit might have been derived from the administration of lidocaine or procainamide either in higher doses or for longer durations before coronary artery ligation.

Secondary Antiarrhythmic Prophylaxis

Secondary prophylaxis refers to administration of antiarrhythmic therapy after the onset of an acute ischemic event. In the present study, neither lidocaine nor verapamil was dramatically or significantly \( (p > 0.10) \) successful in preventing reperfusion ventricular fibrillation when administered after occlusion but before reperfusion. The continuation or supplementation after occlusion of lidocaine, procainamide, or amiodarone treatment that had been initiated before occlusion was also inadequate to protect optimally against reperfusion ventricular fibrillation.

The methods of the present study have also taken into account the spontaneous variability that individual animals demonstrate in their susceptibility to both ligation and reperfusion arrhythmias, whether or not they receive antiarrhythmic therapy. First, by using one large control group, rather than a parallel design with multiple smaller control groups, we could identify subgroups among the controls at widely varying risks for reperfusion ventricular fibrillation. We then calculated the risks for these subgroups based on the arrhythmic events of the antecedent periods of coronary artery ligation. Second, by applying an appropriate statistical method, we could take into account spontaneous differences in the proportions of dogs that fell into these different subgroups. Third, this method of analysis was most helpful in evaluating lidocaine. For example, we observed that lidocaine treatment protocol 1 resulted in seven of the 15 dogs (47%) available for reperfusion in this group having ventricular fibrillation on reperfusion, compared with 36 of 60 (60%) of control dogs \( (p > 0.10) \). On the other hand, lidocaine protocol 2 resulted in only six of 18 of available dogs (33%) having ventricular fibrillation on reperfusion. However, more careful scrutiny revealed that lidocaine treatment protocol 2 was not as efficacious as would have been assumed had one used routine chi-square analysis \( (p < 0.05) \). Rather, this reperfusion group (protocol 2) included disproportionately more dogs (seven of 18) free of ligation ventricular arrhythmias that, therefore, were subsequently at no apparent risk for reperfusion ventricular fibrillation. Furthermore, because lidocaine was not administered until just before reperfusion in protocol 2, one could not ascribe this decreased incidence of ligation arrhythmias to a primary therapeutic effect of lidocaine. Thus, lidocaine was not as efficacious as would have been suggested by routine methods of analysis.

Similarly, the results of other, previous experimental coronary artery ligation or reperfusion studies using relatively few animals (<30 per treatment group) must be interpreted with caution, unless statistical methods were applied that considered not only the variable susceptibility of individual animals to develop ligation and reperfusion ventricular arrhythmias, but more important, that reperfusion arrhythmias are predicated on the arrhythmic events of the antecedent ligation period. Moreover, even a statistically significant arrhythmia reduction might not be adequate clinically if the arrhythmia in question is ventricular fibrillation, as in the present study. However, this model is a severe test of an antiarrhythmic agent and our results are not incompatible with these agents hav-
ing efficacy in other experimental or clinical situations.

Critical to the present analysis was the recognition that different subgroups of animals had different expected incidences for the occurrence of reperfusion ventricular fibrillation, based on the arrhythmic events of the preceding coronary ligation period. Thus, dogs resuscitated from ventricular fibrillation during ligation invariably developed ventricular fibrillation with reperfusion in this model, whereas dogs free of ligation ventricular arrhythmias were at no risk for ventricular fibrillation when reperfused 30 minutes after ligation (fig. 1, table 1), whether or not they received antiarrhythmic therapy. Unfortunately, because so few dogs were in each subgroup (e.g., DVA only, IVA only) we cannot comment on the effects of these various drugs on the different types of ligation ventricular arrhythmias.

Other dogs were at intermediate but predictable risks for developing ventricular fibrillation at the time of reperfusion, based on the occurrence of either IVA, DVA or both during antecedent 30-minute periods of coronary artery ligation. Presumably, differences in ligation and subsequent reperfusion arrhythmias in individual dogs could reflect a heterogeneity of both coronary artery anatomy and of electrophysiologic mechanisms.5, 29-30

Previous animal studies have not considered this heterogeneity sufficiently. Alternatively, some investigators have used more animals, but often with results that were still less than satisfactory.45 The methods of the present study have allowed us to define the risks for subgroups of dogs to develop ventricular fibrillation based on the events engendered by coronary artery ligation. In doing so, we have demonstrated the failure of a variety of antiarrhythmic agents to prevent ventricular fibrillation resulting from reperfusion 30 minutes after acute coronary artery ligation. In addition, although it was not the primary purpose of the present study to evaluate the effects of lidocaine, procainamide or amiodarone on arrhythmias that occur during the antecedent periods of coronary ligation, we did so in order to define the population of dogs subjected to reperfusion. However, using our methods, none of these agents had a significant (p > 0.10) effect on the overall incidence of ventricular arrhythmias or ventricular fibrillation during the 30-minute period of ligation. Previous studies, in which it was also determined that 40–60% of dogs rather than 90% usually develop ventricular fibrillation after ligation of the left anterior descending or circumflex coronary artery, have reported similar results for a variety of antiarrhythmic drugs.17-20, 45-48

One can speculate that the same heterogeneous susceptibility to malignant arrhythmias observed in this experimental animal model may also occur clinically. This may account, in part, for the continued controversy regarding the value of lidocaine prophylaxis in patients presenting to the coronary care unit with an acute ischemic event.48

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