The Efficacy of Antiarrhythmic Agents During Acute Myocardial Ischemia and the Role of Heart Rate

By Ronald R. Hope, M.B., M.R.A.C.P., David O. Williams, M.B., M.R.C.P., Nabil El-Sherif, M.D., Ralph Lazzara, M.D., and Benjamin J. Scherlag, Ph.D.

SUMMARY

The influence of lidocaine, procaine amide, and propranolol on ventricular arrhythmias during acute myocardial ischemia in the dog was examined. Ischemic zone epicardial (IZE) activation delay and the time of onset of ventricular tachycardia (VT₁) were studied. Progressive IZE delay always preceded ventricular tachycardia (VT). Ventricular tachycardia occurred when IZE delay extended into the T wave of the standard electrocardiogram but areas of ischemic epicardium were found in which activation delayed beyond the T wave. Fast heart rates during acute ischemia were associated with an accelerated time course of IZE delay and early VT. Slow heart rates resulted in minimal IZE delay and delayed onset or absence of VT. Sympathectomized dogs with heart rates 32% slower than normal dogs did not develop significant IZE delay or VT during ischemia. When heart rates were increased by atrial pacing, these dogs behaved in the same fashion as the normal dogs with respect to IZE delay and VT. Lidocaine was found to hasten the time course of IZE delay but to have no significant effect on VT₁. Procaine amide did not influence IZE delay nor VT₁ during ischemia. Propranolol slowed the mean heart rate by 20% and appeared to protect against arrhythmia. When the heart rate (115 ± 10 beats/min; mean ± standard deviation) was increased by atrial pacing (184 ± 9 beats/min), propranolol did not significantly influence IZE delay or VT, as compared to the untreated controls. The clinical counterpart of our experiments during acute ischemia may relate to the prehospitalization phase of myocardial infarction.

Additional Indexing Words:
Anesthetized dogs  Propranolol  Lidocaine
Procaine amide  Ventricular activation  Atrial pacing

LIDOCAINE, PROCAINE AMIDE, AND propranolol are frequently used in the coronary care unit to control ventricular arrhythmias thought to lead to ventricular tachycardia and ventricular fibrillation. However, the use of antiarrhythmic agents for the prevention of sudden death¹ ² or in early stages of acute myocardial ischemia has resulted in conflicting clinical³ ⁶ and experimental⁷⁻¹¹ reports indicating either protection or lack of protection from arrhythmias and sudden death. The present study was undertaken to evaluate the efficacy of commonly-used antiarrhythmic agents in the context of acute experimental coronary occlusion in dogs. The clinical counterpart may be the period of acute ischemia in the prehospitalization phase of myocardial infarction.

Since recent studies,¹²⁻¹⁴ as well as this study, emphasize the importance of heart rate in the early stage of acute myocardial ischemia we have paid particular attention to this variable. Most previous drug studies have not considered the role of heart rate in the determination of drug efficacy in preventing fatal ventricular arrhythmias due to acute myocardial ischemia.

Method

Adult mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg) administered intravenously. A Harvard respirator using room air provided mechanical ventilation through a cuffed endotracheal tube. The heart was exposed through the fifth left intercostal space and the pericardium incised. After gentle retraction of the left atrial appendage, a loose ligature was placed around the left anterior descending coronary artery (LAD) within 3–5 mm of its origin.

A standard lead II electrocardiogram was recorded using needle electrodes. Four bipolar subepicardial recording electrodes were placed in the area supplied by the LAD. Each of these electrodes consisted of two stainless steel insulated wires (0.003 inch diameter) threaded through a 25 gauge hypodermic needle. The ends were bent back over the bevel of the needle and cut short to form two small hooks. The needle was then inserted just beneath the epicar-
dium and withdrawn leaving the two wires in place. In one-third of the dogs, a large multipolar “paper” electrode was sutured to the anterior apical epicardium supplied by the LAD. This electrode had two terminals but consisted of multiple bipolar contacts within a 2–3 cm² area. The recording obtained was a composite electrogram of many (10–20) superimposed bipolar electrograms from a relatively large area as compared to the electrograms recorded from the close bipolar wires. A fifth subepicardial bipolar plunge wire electrode was placed away from the area supplied by the LAD and in the region supplied by the circumflex artery. This served as a reference or control electrode. Initial injury effects associated with insertion of the plunge wire electrodes consisted of smaller amplitude electrograms and ST segment changes. These effects subsided after 2 to 5 min and the electrograms remained stable in the absence of LAD occlusion. Injury potentials did not occur with the multipolar electrode as it merely rested on the epicardium.

Stainless steel wires (0.005 inch diameter) were inserted into the left atrial appendage. Control of heart rate was achieved with atrial pacing via stimuli (2 msec duration, 150–200 pulses/min and 2–10 volts) delivered from an S-88 Grass stimulator and Grass 51U 5 isolation units. Two silver wires 0.012 inch in diameter were inserted into the left vagosympathetic trunk in the neck and nerve stimulation (0.05 msec duration, 20 Hz and 1–10 volts) allowed reduction of sinus rate. Control recordings of the electrograms and standard electrocardiogram were made on eight channel Electronics for Medicine recorder at frequencies of 0.05 to 2000 Hz. Recording paper speed was 100 and 200 mm/sec. Recordings were stored on a magnetic tape recorder (Honeywell 5600) and replayed so that selected sections could be registered on photographic paper for detailed analysis.

Procedure

During occlusion, progressive delay of the ischemic zone epicardial (IZE) electrograms in relation to the onset of the QRS complex of the standard ECG was measured in milliseconds (msec). Delay was manifest in both bipolar subepicardial and composite epicardial electrograms, neither of which recorded activation delay in nonischemic areas. Although the delayed activation returned promptly (15–30 sec) to control after the occlusion was released, a period of at least 15 min was allowed between successive occlusions. Ischemic zone epicardial delay was measured from the onset of the Q wave of the standard ECG to the R wave of the electrogram showing maximal delay. Accurately reproducible IZE delay for the same ischemic period at the same heart rates was found in up to 15 temporary LAD occlusions for each dog. The first occlusion however often resulted in earlier IZE delay and arrhythmias. Data were taken only from the second and subsequent occlusions.

LAD occlusions were released at the onset of ventricular arrhythmias. The longest occlusion time was 10 min. Termination of atrial pacing and/or vagal-induced slowing of the heart interrupted frequent ventricular premature beats or ventricular tachycardia (VT), allowing sinus rhythm to resume. Using this technique it was possible to allow repeated LAD occlusions to proceed to VT without consequent ventricular fibrillation (VF) developing. If VF did occur, the experiment was terminated. Defibrillation was not attempted. In all dogs the last occlusion was deliberately maintained so that VT proceeded to VF and death in order to establish that uninterrupted VT invariably degenerated into VF. The time of onset of VT was designated VT₁. With each dog serving as its own control, and with heart rates fixed by atrial pacing, VT₁ in the presence and in the absence of antiarrhythmic drugs was compared. Similarly, the influence of these drugs on IZE delays at various times during ischemia was examined.

Five dogs were subjected to cardiac sympathectomy according to the method of Priola and Fulton. These animals were used in the controlled heart rate experiments and drug studies (see below).

Heart Rate

Ischemic zone epicardial delay and VT₁ were examined during temporary LAD occlusions in ten dogs at four different heart rates (90–120 beats/min, 140–160 beats/min, 170–190 beats/min and 200–230 beats/min; mean ± standard deviation) selected at random. Four of the dogs had been subjected to cardiac sympathectomy.

Lidocaine

In 20 dogs, randomized LAD occlusions were carried out in the presence of lidocaine and compared with control occlusions in the same dogs. Each dog served as its own control. Lidocaine was given as a constant intravenous infusion (5–8 mg/kg/min) throughout the ischemic period commencing one minute prior to occlusion. The infusion dose used was large because constant infusion during the short time of ischemia (3 min, 55 sec, ± 45 sec) would be unlikely to result in stable serum lidocaine levels prior to the onset of arrhythmia. The effects of lidocaine were observed during LAD occlusions when heart rate was held constant at the control paced rate. Occlusions were not performed at uncontrolled rates after lidocaine. In all cases only atrial pacing rates were used at which 1:1 atrioventricular conduction was maintained. Ischemic zone epicardial delay and VT₁ were compared during LAD occlusion in each dog with and without lidocaine. At the conclusion of each experiment, and at least 20 min after the last dose of lidocaine, an additional dose was administered in bolus form (15–20 mg/kg) and each dog was allowed to proceed to VF during LAD occlusion. The heart rate was controlled in these instances.

Procaine Amide

The basic format of these experiments paralleled the lidocaine studies. In ten dogs LAD occlusions were carried out during sinus rhythm (154 ± 12 beats/min) and during atrial pacing (176 ± 7 beats/min). This was repeated at the control atrial pacing rates, 10–20 min after a bolus injection of intravenous procaine amide (10–15 mg/kg). For each dog, IZE delay and VT₁ were compared in the presence and absence of procaine amide during LAD occlusion at the same atrial pacing rate. Finally, and in the presence of a second dose (15–20 mg/kg) of procaine amide, surviving dogs were permitted to proceed to VT and VF. This second dose was administered at least 30 min after the original dose of procaine amide and the atrial pacing rate was the same as during previous occlusions in that dog.

Propranolol

Using propranolol (1–1.5 mg/kg) administered intravenously, VT₁ and IZE delay during LAD occlusion were compared with two or more control occlusions before propranolol was given. Each of ten dogs provided its own control. The effects of atrial pacing at the same rate were observed during LAD occlusions before and 10–20 min after
propranolol was administered. After propranolol it was not always possible to achieve atrial pacing at exactly the same rate as in the control state (150 ± 8 beats/min). Occasionally, heart rates were occasionally observed during LAD occlusions that progressed to VT (fig. 1). In the normal zone electrograms, no delay of activation was seen during ischemia. Maximum IZE delay occurred immediately prior to the onset of ventricular arrhythmias. The mean QT interval of the standard electrocardiogram was 260 msec (range 180–320 msec; heart rates 145 ± 16 beats/min). Figure 2 shows that IZE delays at VT extended into the T wave and in some instances (five of 30 dogs) beyond the QT interval. At no time were ventricular arrhythmias seen without preceding IZE delay. The severity of the IZE delay varied from dog to dog and from one ischemic site to another in the same dog.

However the IZE delay recorded from each individual electrogram was constant for the same period of ischemia during repeated LAD occlusions at the same heart rate. The failure to observe severe IZE delay in all dogs is possibly explained by lack of recording electrodes at the site of maximum delay. In such instances, the bipolar electrodes were removed and reinserted into the ischemic subepicardium and areas of delayed activation found.

In order to avoid the need to use large numbers of bipolar plunge wire electrodes, our composite multipolar electrode was developed. This electrode provides no more information than multiple bipolar plunge wire subepicardial electrodes. However, because of its multiple areas of contact with the epicardium, there is a greater likelihood that areas of delayed epicardial activation will be detected than would be found using three or four close bipolar electrodes. Consequently the composite multipolar electrogram usually showed greater activation delay than individual bipolar subepicardial electrograms (fig. 5) at the same period of ischemia. On occasion a close bipolar electrogram outside the area of the composite electrode showed even greater delay, further illustrating the heterogeneity of activation delay within the ischemic epicardiump.

The effect of heart rate on IZE delay is shown in figure 2. Ten dogs were each subjected to temporary...

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**Figure 1**

The progressive delay of ischemic zone epicardial activation is shown following LAD occlusion. The mean time of VT was 4 min, 20 sec (range: 1 min, 30 sec, to 10 min). Following development of VT, the interval of time from onset of LAD occlusion (O) to onset of ventricular tachycardia (VT) was determined. In each dog the delay in ischemic zone epicardial activation was determined at one-half and three-quarters of the interval to ventricular tachycardia. The filled circles represent the mean value of the maximum ischemic zone activation delay in 30 dogs, with vertical bars depicting the range of values at times 0, VT1/2, VT3/4, and VT. There is no change in time of onset of activation in the normal zone (broken line). The range of QT intervals is indicated by the vertical hatched bar. In five dogs just prior to VT ischemic zone epicardial activation was delayed beyond the QT interval of the standard electrocardiogram.

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**Figure 2**

Effect of heart rate on ischemic zone epicardial activation delay and onset of ventricular tachycardia (VT). Ten dogs were subjected to LAD occlusions at four heart rates (A, 200–230 beats/min; B, 170–190 beats/min; C, 140–160 beats/min, and D, 90–120 beats/min). No dogs developed VT during six minutes of ischemia at the slow heart rates. In contrast, 100%, 90%, and 60% developed VT at rates depicted in A, B, and C, respectively. The average time of onset of VT was 2 min, 20 sec ± 20 sec for curve A; 3 min, 30 sec ± 25 sec for curve B; and 4 min, 30 sec ± 40 sec for curve C.
LAD occlusions at four different heart rates. At the fastest rates (200–230 beats/min) all dogs developed VT rapidly (VT<sub>t</sub> mean, 2 min, 20 sec, ± 20 sec). At heart rates of 170–190 beats/min, nine of ten dogs developed VT (VT<sub>t</sub> mean, 3 min, 30 sec, ± 25 sec). Six of ten dogs developed VT during LAD occlusion at rates of 140–160 beats/min (VT, mean, 4 min, 30 sec, ± 40 sec). None of the dogs developed VT during 6 min of ischemia at heart rates from 90–120 beats/min. In those animals that developed VT the average IZE delay recorded just prior to VT remained essentially the same (140–151 msec) regardless of heart rate or the time at which VT developed (fig. 2).

Four of the above dogs had previously undergone cardiac sympathectomy. The resting sinus rate of these dogs was 95 ± 9 beats/min (32% slower than the average resting heart rates of the normal dogs). This heart rate reduction was of similar magnitude to that reported during chemical sympathectomy by other workers,<sup>10</sup> as well as our own studies using propranolol. When heart rates were increased by atrial pacing, both normal and sympathectomized dogs behaved in the same fashion with comparable IZE delay and onset of ventricular arrhythmias.

Lidocaine

Ischemic zone epicardial delay was measured during 40 randomized LAD occlusions in 20 dogs prior to lidocaine infusion (3–5 mg/kg/min) and compared to 55 control occlusions in the absence of the drug (fig. 3). With the aid of atrial pacing (168 ± 13 beats/min) it was possible to maintain the same heart rate during occlusions before and after lidocaine administration. Control sinus rate (135 ± 16 beats/min) was unchanged after lidocaine (132 ± 11 beats/min). The time of onset of VT during control occlusions (4 min 15 sec ± 40 sec) was slightly greater than during occlusions with lidocaine (3 min 55 sec ± 45 sec). This difference was not statistically significant (P > 0.05). When comparing LAD occlusions with and without lidocaine, differences in IZE delay were not significant until 3/4 VT<sub>t</sub> was reached. At 3/4 VT<sub>t</sub>, average IZE delay in the presence of lidocaine was 78 ± 22 msec as compared to 68 ± 19 msec during control occlusions. The difference is not statistically significant (P > 0.05). At VT<sub>t</sub>, in the presence of lidocaine, mean IZE delay was 166 ± 42 msec. During occlusions without lidocaine, IZE delay at VT<sub>t</sub> was 119 ± 26 msec. The difference is statistically significant (P < 0.02). Thus, although lidocaine did not significantly influence the time of onset of VT, the time course of IZE delay was accelerated. This aspect of our data is discussed later.

Procaine Amide

The resting heart rate in the ten dogs used in this study was 154 ± 11 beats/min. Ten-twenty minutes after the administration of procaine amide, 10–15 mg/kg, the sinus rate was reduced to 140 ± 9 beats/min. Plasma procaine amide concentration achieved ranged from 5.4–18.3 mg/L (mean, 11.4 mg/L). In figure 4, IZE delays and the onset of ventricular tachycardia during acute ischemia before and after procaine amide administration are shown. Atrial pacing at 183 ± 5 beats/min was employed in order to control heart rates in all dogs. In each dog it was possible to pace at the control rate after procaine amide administration. The time of onset of VT during control occlusions was 3 min, 25 sec ± 35 sec as compared with 3 min, 35 sec ± 30 sec during occlusions with procaine amide. The difference is not significant (P > 0.05). At VT<sub>t</sub>, the control IZE delay was 124 ± 21 msec as compared with 145 ± 33 msec during occlusions with procaine amide. Thus IZE delay was not appreciably influenced (P > 0.25) by procaine amide. Figure 5 shows records from one of the dogs used in these experiments.

Propranolol

Propranolol resulted in an over-all heart rate
HEART RATE, DRUGS, AND ISCHEMIA

The time of onset of VT during control LAD occlusions (VT = 3 min, 25 sec, ± 35 sec) was not significantly altered after procaine amide administration (VT PA = 3 min, 35 sec, ± 30 sec). Ischemic zone epicardial activation delay also was not significantly influenced by procaine amide.

Figure 4

Effect of procaine amide on ischemic zone epicardial activation delay and time of onset of ventricular tachycardia (VT) in ten dogs. The average of beats/min. after procaine amide.


during sinus rhythm (mean 145 ± 12 beats/min) only two of ten dogs developed VT during 6 min of ischemia (curve C). After propranolol (curve D) the average sinus rate was reduced to 115 ± 10 beats/min and in no instance did VT occur and only minimal IZE delays occurred during 6 min of ischemia. However, when the ventricular rate was increased and controlled by atrial pacing in eight dogs and by His bundle pacing in two, propranolol did not prevent the progression of IZE delay. Thus at comparable heart rates the IZE delay at the onset of VT was 118 ± 17 msec during control occlusions, and 123 ± 26 msec in the presence of propranolol. These differences were not significant (P > 0.05). The time of onset of VT in the absence of propranolol was 3 min, 35 sec, ± 20 sec and 3 min, 45 sec, ± 25 sec during occlusions with propranolol. The difference is not significant (P > 0.05). The atrial pacing rate was 190 ± 8 beats/min in control occlusions and 184 ± 9 beats/min after propranolol. Second degree atrioventricular block induced by propranolol prevented pac

ning at control rates in some dogs. His bundle pacing in the presence of propranolol in two animals resulted in pacing at control rates.

Discussion

In spite of the extensive literature related to pharmacological aspects of arrhythmia treatment in myocardial infarction, the efficacy of antiarrhythmic agents during acute myocardial ischemia has not been established. There is evidence that arrhythmias developing within the first few minutes of ischemia differ in their pathogenesis from arrhythmias arising later.18–24 It is thought that increased automaticity in the myocardium is largely responsible for arrhythmias occurring in the late ischemic period or after established infarction. The earlier arrhythmias may develop on a re-entry basis. Most drug studies have been concerned with suppression of arrhythmias in the late ischemic period. It is conceivable that antiarrhythmic agents effective in the setting of chronic ischemia or infarction may not necessarily be useful during the initial ischemic period. For example, Gamble and Cohn9 have found propranolol, procaine amide, and lidocaine to be “more effective in normalizing automaticity than in abolishing reentry.”

It is generally agreed that there is a high, albeit variable, incidence of early fatal ventricular arrhythmias following abrupt LAD occlusion in dogs.8,25 In order to accurately compare the efficacy of various antiarrhythmic agents in the early phases of ischemia we have found the delay of activation in ischemic zone epicardial and subepicardial electrograms to be of value. This activation delay has previously been reported by others in the setting of chronic ischemia26 and infarction.27 However, the greater degree and more rapid progression of IZE delay in early ischemia has only recently been documented.12 Ventricular arrhythmias are invariably preceded by significant IZE delays (fig. 2). It should be emphasized that the time of activation in local areas of the ischemic myocardium may vary widely following LAD occlusion. However, those areas showing maximum delay equalled or exceeded the QT interval. Thus the heterogeneity of conduction and marked delay of activation within the ischemic zone establishes the conditions necessary for re-entry.

When heart rates were controlled, neither lidocaine (fig. 4) nor procaine amide (fig. 5) prevented IZE delays after acute LAD occlusions nor was the coincident onset of ventricular arrhythmia significantly influenced. Stevenson et al.8 found a higher incidence of ventricular fibrillation after lidocaine during acute ischemia in dogs. Lidocaine has also been found to accentuate ventricular re-entry in cats.9 Our results indicate that lidocaine does not significantly influence

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Failure of procaine amide to influence delay of ischemic zone epicardial activation and onset of ventricular arrhythmia during acute ischemia is shown in this record from one of ten dogs used in the procaine amide experiments. L-2 = standard electrocardiogram lead 2; Cp IZeg = composite electrogram or multipolar electrogram; IZ eg (1) and IZ eg (2) = ischemic zone subepicardial electrograms; Nz eg = normal zone subepicardial electrogram. Control recordings obtained prior to LAD occlusion are shown on the left. Recordings at 2 min and 2 min 30 sec of ischemia show delayed activation of ischemic zone epicardial electrograms, diminished amplitude, and increased duration. The normal zone electrograms remained unchanged. After 3 min of ischemia, VT occurs (last 6 beats) and is suppressed after vagal-induced atrial arrest. A control recording taken during ligation and 30 min prior to administration of procaine amide showed an identical time course of IZE delay and the same time of onset of VT.

The time of onset of VT during acute ischemia. Ischemic zone epicardial delay however was greater just prior to the onset of VT in the presence of lidocaine (fig. 4). These data indicate that the association between increasing IZE delay and the onset of ventricular arrhythmias may not necessarily be a primary relationship. Other factors may be important. For example, the response of the surrounding normal muscle to early activation may be depressed by lidocaine so that more IZE delay is necessary in order to activate the normal muscle.

Recently, Spear et al.11 using small doses of lidocaine (0.7 mg/kg) have shown an increase in ventricular fibrillation threshold during acute ischemia. This technique initiates VF with an induced ventricular premature stimulus falling in the T wave but ignores the conditions necessary for the actual initiation of such premature beats. Previous work from our laboratory has shown that in the setting of acute ischemia with marked dispersion of activation, ventricular premature beats falling late in diastole can cause VT and VF.28 Therefore, the physiological relevance of the ventricular fibrillation threshold is open to question and the efficacy of antiarrhythmic agents as determined by this technique may be misleading. Our study focuses attention on the ability of commonly-used antiarrhythmic agents to inhibit spontaneous ventricular arrhythmias during acute ischemia. Thus, we believe our method of drug evaluation may permit more direct comparison with the clinical situation.

As with lidocaine, the antiarrhythmic efficacy of procaine amide in established myocardial infarction is well accepted.29 However, using procaine amide in the setting of acute ischemia, we have found neither prevention of, nor delay in the onset of early ventricular arrhythmias. Kosowsky et al.,1 discussing the prophylactic use of procaine amide, cite unpublished data of their own in which the incidence of ventricular fibrillation in an unstated number of dogs was reduced from 72 to 17% during acute ischemia. However, no reduction in the incidence of ventricular premature beats and ventricular arrhythmias was noted. The ventricular arrhythmias did not degenerate into fibrillation. Heart rates before or after drug administration were not detailed.
The effects of LAD occlusion were determined under control conditions (curves A and D) and following propranolol administration (curves B and C) in ten dogs. The effects of LAD occlusions were compared when the heart rate was held constant by atrial pacing (170–200 beats/min) (curves A and B) and when spontaneous sinus rhythm was present (curves C and D). During sinus rhythm the values of ischemic zone epicardial activation delay were obtained at the same interval of time following LAD occlusion as those obtained during atrial pacing. During atrial pacing, the rate of onset of VT and the extent of ischemic zone epicardial activation delay was not appreciably influenced by propranolol. However, during sinus rhythm (curve C), at an average rate of 145 ± 12 beats/min, only two of the ten control dogs developed VT during 6 min of ischemia. After propranolol (curve D) the average sinus rate was reduced to 115 ± 10 beats/min, and in no instance did ventricular tachycardia occur.

Lidocaine in the dosages used in the present study did not significantly influence heart rates. Procaine amide reduced the heart rate by approximately 9%. However, propranolol (fig. 6) resulted in an average heart rate reduction of 20%. With the latter drug, IZE delay during LAD occlusions in sinus rhythm was minimal and no dogs developed VT during 6–10 min of ischemia. Constant atrial pacing overcame the heart rate effect of propranolol (in two dogs His bundle pacing was used because of A-V block) and IZE delay during ischemia was not significantly different from control. The time of onset of ventricular tachycardia was not changed (fig. 6).

The deleterious effects of increased heart rate on the incidence of arrhythmias in acute ischemia has been emphasized by several workers. Norris et al. have found the same situation to exist in the clinical setting. These workers found that the mortality incidence in patients with acute myocardial infarction having sinus bradycardia was 6% and those with sinus tachycardia 26%. Those who had neither bradycardia nor tachycardia showed a 15% mortality incidence. In many studies relating to the antiarrhythmic effects of drugs in acute ischemia, the effect of heart rate change has not been appreciated. In fact, many of the conclusions reached in large studies by Stephenson et al., and more recently by Khan et al., should be viewed in the context of uncontrolled heart rate variation. In the latter studies, awake dogs were used and the control response to LAD occlusion showed an abrupt increase in heart rate from an average of 120 beats/min before occlusion to greater than 180 beats/min by one minute after occlusion. The incidence of VF in these control dogs was 72%. In the experimental dogs subjected to treatment with various antiarrhythmic agents, the four groups showing a decreased incidence of VF (20% or less) had the lowest average initial heart rates. The effect of heart rate is also well shown in studies by Kaumann and Aramendia. The beta-adrenergic blocking agent MJ 1999 reduced the incidence of ventricular fibrillation in dogs during acute ischemia. However, with the alternative use of “reserpinized” dogs they concluded that the antiarrhythmic effect was not directly related to the beta-adrenergic blocking action of MJ 1999. Their data reveal an average heart rate reduction of up to 44%. These results parallel our present studies which show a heart rate reduction of 20% and no arrhythmias during sinus rhythm after propranolol. However, with the aid of atrial pacing and in some cases His bundle pacing, we have demonstrated that the protective influence of propranolol during acute ischemia is due entirely to its negative chronotropic effect. In this regard it has been reported that cardiac sympathetic denervation prevents ventricular arrhythmias associated with acute ischemia. From our own experience, with dogs subjected to LAD occlusion, we found that denervation protected against arrhythmia because heart rates were slower. The sympathectomized animals behaved exactly like normal dogs during acute ischemia when their slow resting heart rates had been increased by atrial pacing to the same level of heart rates as in the normal dogs. We must emphasize that we did not set out to examine the effects of bradycardia. It cannot simply be assumed from our data that further slowing of the heart rate below 90 beats/min imparts greater protection from arrhythmias during acute ischemia. A recent study indicates that both fast and slow heart rates may be associated with an increased incidence of arrhythmias during acute myocardial ischemia in the dog.

It must be emphasized that our studies using lidocaine, procaine amide, and propranolol apply only to arrhythmias occurring within the first few minutes after coronary artery occlusion in the dog. Our data may relate to the prehospitalization phase of patients with myocardial ischemia or infarction. Nevertheless it is possible that differences in electrophysiological
events during acute ischemia may exist between man and the anesthetized open-chest dog. If extrapolation of our data to the clinical setting is appropriate, we would postulate that antiarrhythmic agents useful in the first few minutes of myocardial ischemia would be those which prevent heart rate increases due to sympathetic activity, with or without lowering of resting heart rates. Our results indicate that neither lidocaine nor procaine amide prevent arrhythmias during acute ischemia and that propranolol and cardiac sympathetic denervation do so mainly by a reduction of heart rate.

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RONALD R. HOPE, DAVID O. WILLIAMS, NABIL EL-SHERIF, RALPH LAZZARA and BENJAMIN J. SCHERLAG

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