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Pranolium

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Sudden coronary death is a major cause of mortality in the United States today. As many as 199,000–386,000 (12) individuals may die suddenly each year, with the majority of these deaths resulting from ventricular fibrillation secondary to ischemic heart disease (64). This makes the management of ventricular rhythm disorders in patients with ischemic heart disease and the prevention of sudden coronary death a high priority for pharmaceutical research and drug development. While there are many drug agents currently available for the treatment and suppression of chronic ventricular arrhythmias, no studies have been conducted to date as to the effectiveness of suppression of ventricular arrhythmias in reducing mortality due to sudden coronary death. In addition, no currently available antiarrhythmic agent has the combined properties of low toxicity and proven efficacy for the prevention of sudden coronary death which is most often due to ventricular fibrillation.

One group of drugs that has been studied for its ability to prevent sudden death is the beta-blockers. Both alprenolol (1,2,86) and practolol (48,49) have been found to reduce mortality when given to patients following a myocardial infarction. However, in other studies, practolol (7), propranolol (8,54,84), atenolol (84), and oxprenolol (85) have been reported to be ineffective in reducing the incidence of sudden coronary death in post-myocardial infarction patients. It should be emphasized that in none of the above studies was the relationship between the suppression of ventricular arrhythmias and sudden death examined.

Recently, there has been new interest in the beta-blockers with the publication of a report on timolol (55). This agent was shown to reduce both total mortality and mortality due to sudden cardiac death, once again suggesting that beta-adrenergic blockade may protect patients at risk of sudden coronary death. However, the interruption of adrenergic support to the heart by the general use of beta-adrenergic blocking agents may not be without hazard in those patients who require a degree of cardiac inotropic and chronotropic support during the acute phase of myocardial infarction. Such patients may be subject to a higher incidence of cardiogenic shock and bradyarrhythmias. Furthermore, beta-adrenergic receptor blockade might preclude the successful use of inotropic agents such as norepinephrine or dopamine. Other limitations to the use of beta-receptor blocking agents would be those patients with obstructive airway disease and those with heart failure.

Since beta-adrenergic receptor blockade may not be essential for the antiarrhythmic actions of "membrane stabilizing" beta-blockers such as propranolol, one approach to the above problem would be to design a pharmacologic agent with the beneficial electrophysiological properties of the beta-adrenergic blocking agents, but without the ability to inhibit the beta-adrenergic receptor.

This chapter describes the electrophysiologic and pharmacologic properties of pranolium ([*N*,*N*-dimethyl-1-isopropylamino-3-(1-naphthyloxy)-propran-2-ol]); UM-272, SC-27761 (Fig. 1), the dimethyl quaternary derivative of propranolol. Pranolium has been demonstrated to be an effective antiarrhythmic agent when tested against a variety of experimentally induced cardiac arrhythmias while possessing no beta-adrenergic blocking activity nor showing any local anesthetic activity. In addition, data presented in this chapter suggest that pranolium may be an effective agent in the treatment of sudden coronary death.

IN VITRO ELECTROPHYSIOLOGY

The only microelectrode study published to date on the electrophysiology of pranolium is that of Rosen et al. (67). These workers found pranolium's electrophysiologic properties to closely resemble those of propranolol in canine Purkinje fibers. At a concentration of 10^{-5} M, pranolium produced a time-dependent decrease in action potential amplitude and in the maximum rate of depolarization (V_{max}), a slight decrease in resting membrane potential, and a shortening of the action potential duration (APD) as measured at 50% repolarization (Fig. 2). Propranolol produced the same qualitative alterations in the action potential of similar or greater magnitude than pranolium and in a shorter time period. The effects of pranolium were also dose related, as 10^{-6} and 10^{-7} M pranolium exerted lesser effects on the action potential than the 10^{-5} M concentration. Pranolium, 10^{-5} M, also decreased V_{max} at all levels of membrane potential (Fig. 3), and this was related to a 1.50-fold increase in conduction time. The effective refractory period (ERP) was decreased slightly by pranolium, but APD was decreased to a greater degree than ERP, resulting in an increase in the ERP relative to the APD. This also resulted in an increase in the activation voltage of the earliest propagated premature beat (that beat occurring just at the ERP) despite the fact that repolarization was more fully complete at the time of the earliest premature beat.

Automaticity in canine Purkinje fibers was reduced by pranolium via a reduction in the slope of phase 4 depolarization. However, pranolium, 10^{-6} M, was not able to block the increase in spontaneous rate due to the addition of 8μg of epinephrine to the bathing medium. In contrast, propranolol at 5×10^{-7} M was fully effective

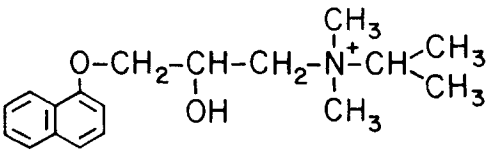

FIG. 1. Structure of pranolium (UM-272; SC-27761).

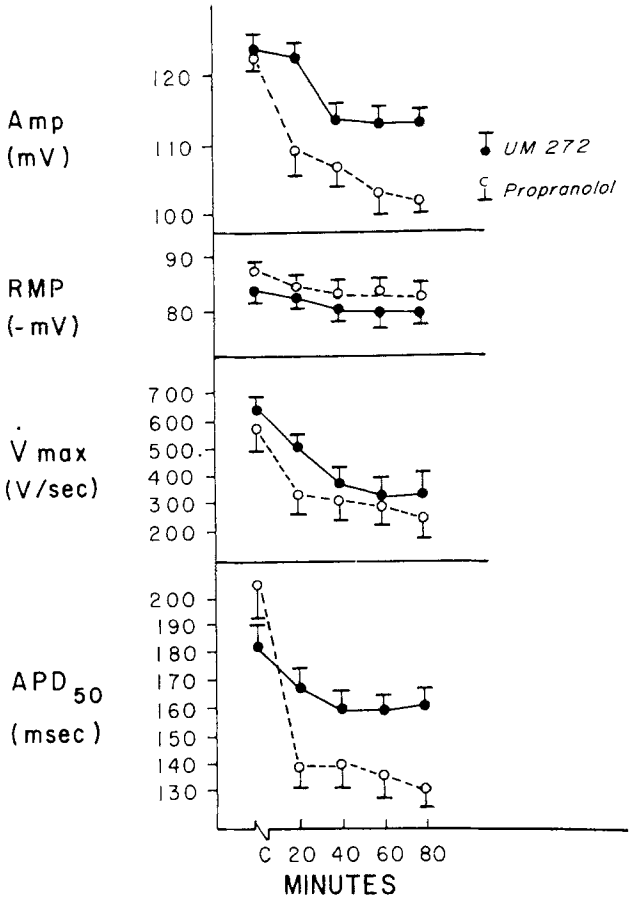

FIG. 2. Effects of pranolium, 10^{-5} M, and propranolol, 10^{-5} M, on action potential characteristics. *Vertical axis:* action potential amplitude, resting membrane potential, V_{max}, and duration to 50% repolarization. *Horizontal axis*: time. Mean ± SE of eight experiments with pranolium and six experiments with propranolol. $[K^+]o$ = 4 mM. Temp. 36–37°C; cycle length 800 msec. (From Rosen et al., ref. 67, with permission.)

in antagonizing the increase in rate produced by epinephrine, suggesting that pranolium lacks beta-adrenergic blocking properties.

Microelectrode data from our laboratory *(unpublished observations)* tend to support the findings of Rosen et al. (67), at least in so far as pranolium's ability to decrease V_{max}. Figure 4 shows a control recording of an action potential and its first derivative from canine ventricular muscle both before and after 5×10^{-5} M of pranolium. Note that the presence of pranolium shortened the APD and decreased V_{max}. However, in our study, 10^{-4} M pranolium had little effect on canine Purkinje fiber APD, but produced a definite increase in the ERP (Fig. 5). The reason for this discrepancy in the effect of pranolium on ERP is not certain, but may be the result of the different concentrations used (10^{-5} versus 10^{-4} M). The concentration

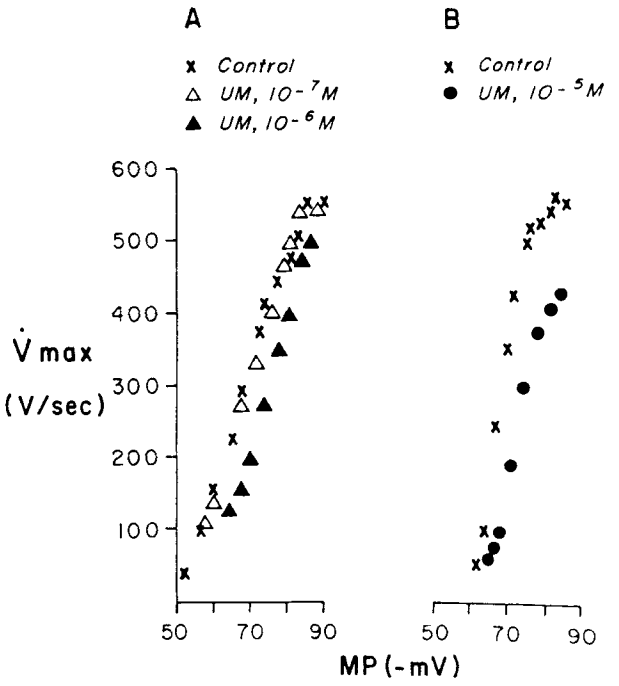

FIG. 3. Effects of pranolium on membrane responsiveness. Temp. 37°C. *Vertical axis:* V_{max} (volts/sec). *Horizontal axis:* membrane potential (millivolts). Perfusion period, 20 min. (From Rosen et al., ref. 67, with permission.)

of 10^{-4} M used in our laboratory more realistically reflects the tissue concentration of pranolium found in the heart after an intravenous dose of 5 mg/kg. This is an effective antiarrhythmic dose of pranolium and results in a myocardial concentration of 34–36 μg/g tissue (see section below on Pharmacokinetics). In addition, the overwhelming amount of *in vivo* electrophysiologic data indicate that pranolium prolongs ERP (see below). For this reason it is our conclusion that, based on microelectrode studies, pranolium's major electrophysiologic effects are to decrease V_{max} and conduction velocity and increase refractoriness.

An *ex vivo* study reported by Dresel and Potter (13) found pranolium to decrease conduction velocity in atria, AV node, and the ventricles of isolated blood perfused dog hearts. Both propranolol and pranolium (but not practolol) produced dose-related increases in the minimal conduction time (MCT) of the AV node in response to late premature stimuli. The increase in conduction times noted with the two larger doses of pranolium (2–4 mg/kg) was not statistically significant due to the large variability among hearts. At 1 mg/kg pranolium produced, however, a significant increase in conduction time. At 1, 2, and 4 mg/kg pranolium produced, on the average, an increase in AV conduction time. In addition, pranolium produced a nonparallel shift to the right of the curve relating AV conduction to the degree of prematurity of extrasystoles (ACT). This means that in the presence of pranolium

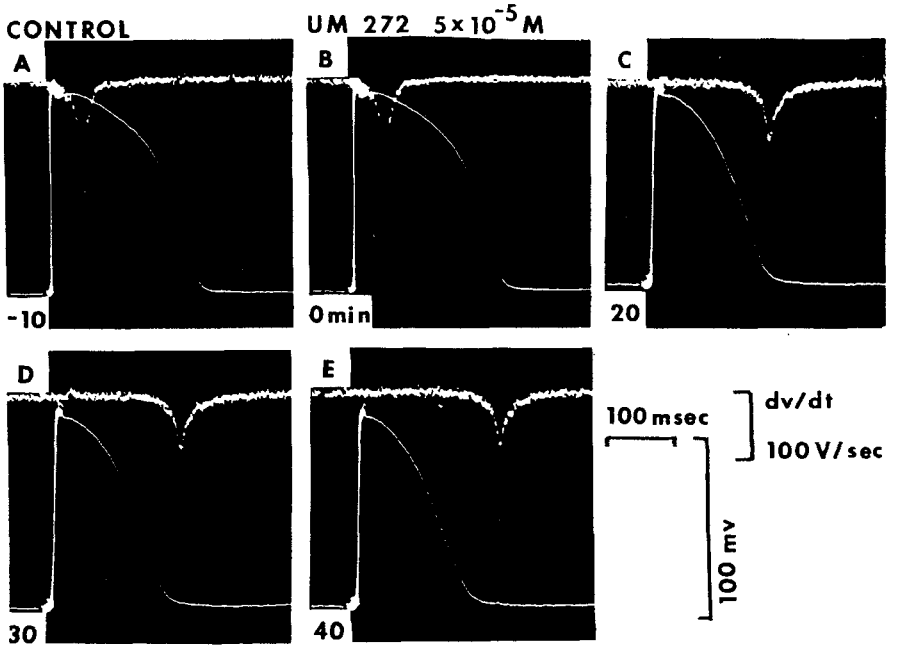

FIG. 4. Transmembrane recordings from a canine ventricular muscle cell **(lower traces)** and the corresponding *dv/dt* of phase 0 **(upper traces)** before and after administration of pranolium. Note shortening of action potential and reduction in maximum *dv/dt*.

(2 mg/kg), late but not early extrasystoles were conducted at a slower rate through the AV node than in the absence of pranolium. In this respect, pranolium resembles methyl lidocaine which also produces a nonparallel shift to the right in the ACT curve (43). Propranolol, on the other hand, produces a small, parallel rightward shift in the ACT curve, indicating that propranolol decreases the conduction of both late and early extrasystoles. Practolol had no effect on the ACT curve, indicating that the effect of propranolol and pranolium on this relationship was not due to beta-adrenergic receptor blockade.

Interestingly, Dresel and Potter found that neither propranolol (2 mg/kg) nor practolol (0.5–4 mg/kg) affected impulse conduction in either atrial or ventricular muscle. Pranolium, however, produced a dose-related decrease in both atrial conduction (as measured by the increase in time from the pacing stimulus artifact to the atrial electrogram on a His bundle recording) and ventricular conduction (as measured by the increase in time from the His bundle depolarization to the ventricular electrogram).

That the actions of pranolium on conduction are not related to a local anesthetic action of this drug has been shown by Schuster et al. (71). These workers have studied the comparative effects of 10^{-3} M of both pranolium and propranolol on intact and desheathed frog sciatic nerve (Fig. 6). Note that while propranolol produced a time-dependent decrease in the nerve monophasic spike potential, pranolium

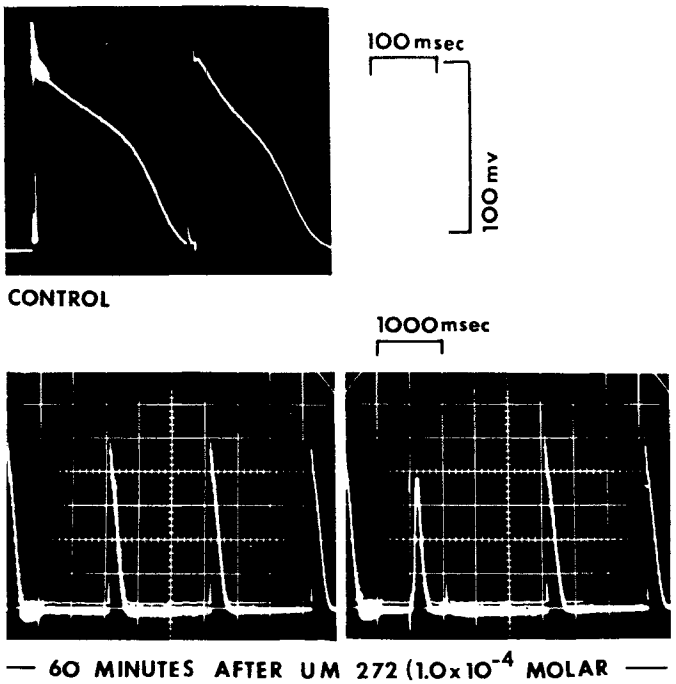

FIG. 5. Transmembrane potential recordings from canine Purkinje fiber paced at 1500 msec cycle length. **Top trace** at fast sweep speed shows minimal interval for propagated response (effective refractory period) is 230 msec in the control state. **Lower left trace** was photographed at slow sweep speed and shows the response to pacing at a 1500 msec cycle length 60 min after administration of pranolium. **Lower right trace** shows that effective refractory period is increased to 1010 msec.

produced no change in the spike potential in either intact or desheathed nerves. So, while pranolium clearly alters conduction and refractoriness in canine myocardial tissue, these effects are not related to any local anesthetic properties of the drug. Additionally, the *in vitro* electrophysiological properties of pranolium occur despite the absence of beta-adrenergic receptor blocking action.

IN VIVO ELECTROPHYSIOLOGY

The results of *in vivo* studies with pranolium are consistent with the drug's *in vitro* actions. In the initial work of Kniffen et al. (35), pranolium produced a dose-related prolongation of ventricular ERP and AV nodal functional refractory period (AVFRP) and an increase in AV conduction time. Figure 7 and Table 1 summarize the data demonstrating the ability of pranolium to increase ventricular refractoriness in the anesthetized dog. Pranolium elevates the ventricular ERP at 5 and 10 mg/kg and shifts the ventricular strength-interval curve progressively to the right without altering diastolic excitability. A similar effect of pranolium on refractoriness is seen on the AV node (Tables 2 and 3). Pranolium, 2–8 mg/kg, progressively increases

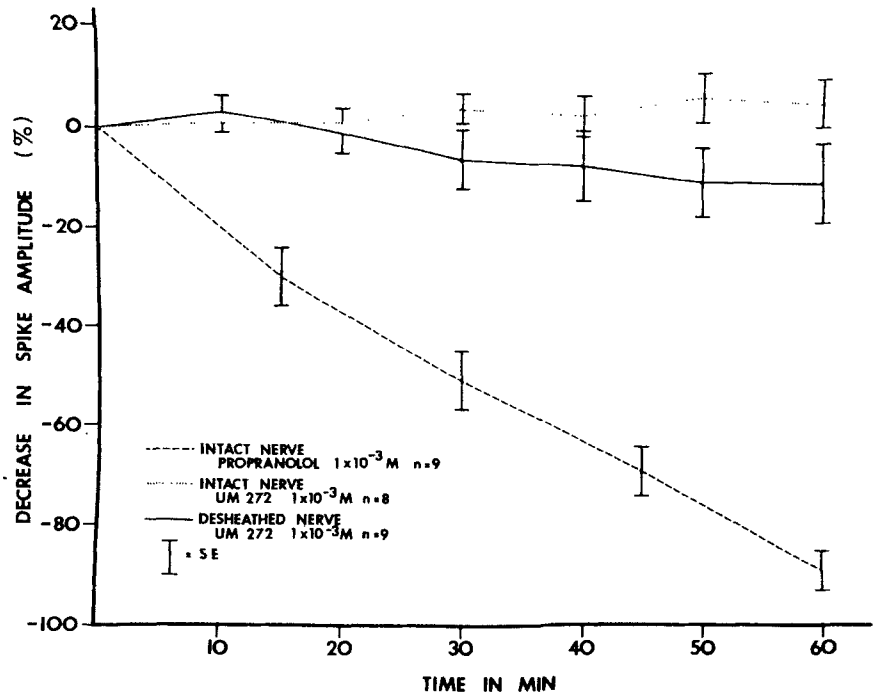

FIG. 6. The effects of propranolol, 10^{-3} M, and pranolium (UM-272), 10^{-3} M, upon spike amplitude in the frog sciatic trunk. Experiments with propranolol were performed on intact nerves and pranolium was tested in both the intact and desheathed nerve preparations. Results are plotted as the percentage decrease in the overall amplitude of the nerve spike potential. Unlike propranolol, pranolium did not cause a significant decrease in spike amplitude over the course of 1 hr in either preparation. Pranolium is devoid of local anesthetic activity. (From Schuster et al., ref. 71, with permission.)

the AVFRP and this results in a decrease in the maximum following rate of the AV node to atrial pacing. While in the control state, the maximum pacing rate was 291.9 ± 6.5 (mean ± SEM) beats/min; after 8 mg/kg this maximum rate decreased to 212.2 ± 3.1 beats/min, a decrease of 39%. Note that there is good agreement between the increase in AVFRP calculated from the maximum driving rate in Table 3 and the actual increase in AVFRP determined by the atrial premature systole technique (Table 2). Pranolium at 8 mg/kg was also found to significantly increase AV conduction time from a control value of 146.8 ± 5.2 msec to a maximum value of 245.0 ± 5.0 msec.

When studying the actions of pranolium on automaticity, Kniffen et al. (35) found pranolium to decrease both spontaneous SA nodal and atrial and ventricular automatic activity. In 5 dogs in which the SA node had been crushed, 3 mg/kg of pranolium lowered the AV junctional rate from 76.2 ± 11.6 beats/min to 50.8 ± 6.3 beats/min and a second dose of 3 mg/kg further reduced the rate to 37.0 ± 5.2 beats/min. AV junctional escape time, defined as the interval between the last electrically driven beat and the first nondriven QRS complex, was also prolonged,

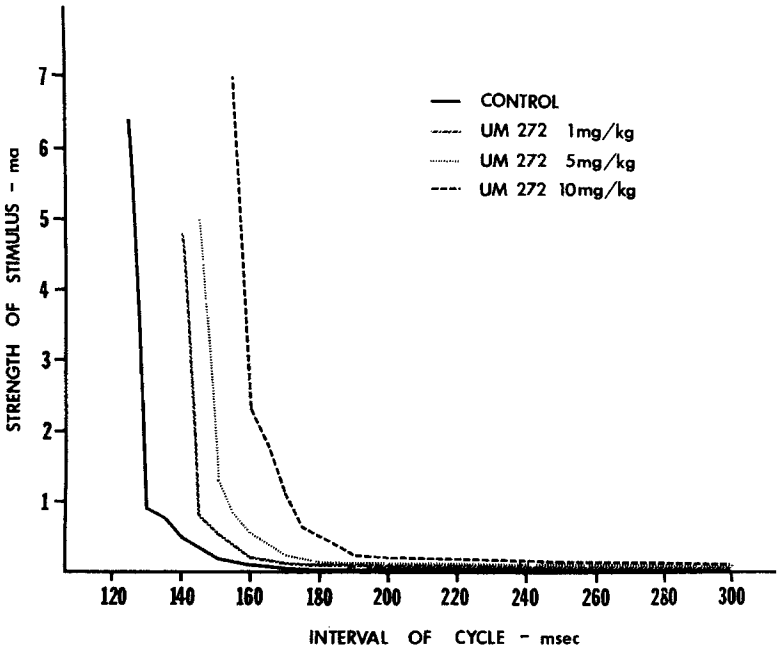

FIG. 7. Effect of pranolium on the canine ventricular strength-interval curve. The *abscissa* shows the time interval between the last paced beat and the premature test impulse. The *ordinate* expresses the strength of the test impulse in milliamperes. This example shows that increasing doses of pranolium successively shift the ventricular strength-interval curve to the right by increasing the effective refractory period without changing the diastolic threshold to excitation. (From Kniffen et al., ref. 35, with permission.)

TABLE 1. *Effect of pranolium on the ventricular strength-interval curve*

	Effective refractory period (msec)			
		After pranolium at mg/kg, i.v.		
Exp. No.	Control	1.0	5.0	10.0
1	107	110	115	125
2	110	115	125	140
3	125	135	145	150
4	115	110	125	135
5	125	140	145	160
M ± SE	116.4 ± 3.7	122.0 ± 6.4	131.0 ± 6.0[a]	142.0 ± 6.0[b]

[a] $p < .005$.
[b] $p < .001$.

TABLE 2. *Effect of pranolium on the AV functional refractory period and conduction time studied by the atrial premature systole technique* (N = 5)

	AV Conduction			AV Functional refractory period		
	Time (msec)	% Change	*p* Value	Time (msec)	% Change	*p* Value
Control	146.8 ± 5.28			210.8 ± 10.96		
Pranolium, i.v.						
2.0 mg/kg	175.6 ± 6.43	19.6	<.001	241.2 ± 13.24	14.4	<.005
4.0 mg/kg	190.6 ± 7.87	29.8	<.001	250.4 ± 12.09	18.8	<.001
8.0 mg/kg	245.0 ± 5.00	43.8	<.001	275.7 ± 18.20	30.8	<.010

TABLE 3. *Effects of pranolium on the functional refractory period as determined from the maximum AV transmission rate* (N = 5)

Drug	Max. rate of AV transmission (beats/min ± SE)	Functional refractory period		
		Calculated time ± SE (msec)	% Change	*p* Value
Control	291.9 ± 6.5	205.9 ± 4.8		
Pranolium, i.v.				
2.0 mg/kg	253.2 ± 9.0	238.2 ± 8.8	15.7	<.05
4.0 mg/kg	235.7 ± 10.4	256.4 ± 10.8	24.5	<.005
8.0 mg/kg	212.2 ± 13.1	286.8 ± 16.3	39.3	<.005

from a control value of 2.9 ± 1.5 to 6.9 ± 2.2 ($p < .05$) sec after the first dose of 3 mg/kg and to 12.6 ± 3.4 ($p < .05$) sec after the second dose of 3 mg/kg of pranolium. In dogs in which a suture was placed through AV junctional tissue near the bundle of His, both atrial and ventricular rate could be studied independently. Each of two doses of 3 mg/kg of pranolium effectively reduced both atrial and ventricular rate, confirming the *in vitro* work and demonstrating that pranolium decreases automaticity in the SA node, atria, as well as ventricular myocardium.

More recently, pranolium has been shown to alter refractoriness and conduction in ischemic myocardium. Gibson et al. (15) studied the effect of the drug on the ERP and on ventricular activation times (AT) in both normal and acutely ischemic myocardium in the anesthetized dog. Ischemia was produced by occlusion of selected diagonal branches of the left anterior descending coronary artery (LAD), and stainless steel bipolar electrodes were placed in the area previously perfused by the occluded vessel (IZ) and in the area perfused by the nonoccluded left circumflex artery (NZ). Table 4 presents the data showing the effects of two different doses of pranolium as compared with saline-treated controls (see legend for dose). In saline-treated dogs, occlusion of an LAD diagonal branch produced an immediate

TABLE 4. *Effect of pranolium on the effective refractory periods of ischemic and nonischemic myocardium*

Min after occlusion[a]	Group A (9)		Group B (5)		Group C (7)	
	NZ (msec)	IZ (msec)	NZ (msec)	IZ (msec)	NZ (msec)	IZ (msec)
0	146 ± 4.9	143 ± 3.9	168 ± 2.9	164 ± 1.7	201 ± 15.6	209 ± 7.5
10	147 ± 5.0	130 ± 3.9[b,c]	169 ± 2.4	179 ± 6.7[b,c]	196 ± 13.5	243 ± 11.1[c]
20	148 ± 4.8	124 ± 2.7[b,c]	168 ± 3.0	177 ± 7.2	198 ± 14.5	224 ± 6.3[b]
30	149 ± 4.6	120 ± 3.0[b,c]	166 ± 2.8	165 ± 4.9	192 ± 14.5	219 ± 6.9[b]
40	148 ± 4.3	120 ± 3.8[b,c]	166 ± 2.8	161 ± 5.2	190 ± 13.4	219 ± 7.1[b]
50	149 ± 5.0	120 ± 5.4[b,c]	164 ± 3.8	153 ± 5.6	188 ± 13.4	216 ± 6.5[b]
60	149 ± 5.2	118 ± 6.4[b,c]	163 ± 4.6	156 ± 5.8	187 ± 13.8	216 ± 6.9[b]
80	148 ± 5.3	120 ± 7.0[b,c]	163 ± 4.7	158 ± 5.7	190 ± 14.1	208 ± 9.1
100	147 ± 5.2	120 ± 7.0[b,c]	163 ± 3.2	163 ± 3.2	188 ± 14.3	208 ± 8.5
120	146 ± 5.8	126 ± 6.7[b,c]	162 ± 3.8	166 ± 2.9	185 ± 13.4	211 ± 8.5

NZ, nonischemic myocardium; IZ, ischemic myocardium; group A, saline treatment; group B, pranolium, 5 mg/kg bolus and 25 μg/kg/min infusion; group C, pranolium, 10 mg/kg bolus and 50 μg/kg/min infusion. Numbers in parentheses are numbers of experiments.

[a]Thirty minutes post-treatment.

[b]$p < .05$; IZ, 0 min compared to test.

[c]$p < .05$; IZ compared to NZ.

decrease in IZ ERP while no changes occurred in the NZ. In contrast, after pranolium, control ERP was considerably prolonged, and after occlusion the IZ ERP was either greater than or the same as the NZ ERP, indicating that pranolium had decreased the disparity in refractoriness between the normal and the ischemic myocardial regions. Additionally, pranolium increased ventricular AT prior to occlusion and both doses of pranolium significantly elevated AT in the IZ after occlusion (Table 5), indicating that pranolium was preferentially slowing myocardial conduction in the IZ.

Patterson and Lucchesi (62) made similar observations in the chronically ischemic, conscious dog subject to programmed electrical stimulation. Figure 8 depicts the effect of pranolium (5 or 10 mg/kg) after chronic administration for 2 days (days 3 and 4) followed by withdrawal of the drug on day 5. Dogs had previously undergone experimentally induced myocardial infarction by a 90-min occlusion of the LAD followed by reperfusion through a critical stenosis. When the values on days 3 and 4 are compared with those on day 5 (drug withdrawal), pranolium produced considerable prolongation of the ERP and an increase in IZ and NZ Q-EG-interval (defined as the interval between the Q wave of the lead II ECG and the major deflection of the bipolar electrogram, a measure of conduction). These increases in conduction time and refractoriness were associated with a decrease in the severity of the arrhythmic response of pranolium-treated dogs to programmed electrical stimulation as compared with nontreated controls.

To summarize, pranolium, both *in vitro* and *in vivo* increases conduction time as a result of its ability to decrease the V_{max} of the AP. In addition, pranolium

TABLE 5. *Effect of pranolium on activation time in ischemic and nonischemic myocardium*

Min after occlusion	Group A (6)		Group B (5)		Group C (6)	
	NZ[a] (msec)	IZ (msec)	NZ (msec)	IZ (msec)	NZ (msec)	IZ (msec)
0	−1 ± 1.0	−1 ± 0.6	5 ± 1.4	3 ± 1.1	14 ± 2.4	6 ± 1.8
10	0 ± 1.1	−9 ± 3.4[b]	7 ± 2.1	16 ± 5.9[b]	14 ± 2.5	19 ± 11.0
20	−2 ± 1.2	4 ± 3.5	6 ± 1.9	13 ± 4.4[b]	12 ± 3.5	16 ± 8.8
30	0 ± 1.8	2 ± 2.9	8 ± 2.1	13 ± 4.2[b]	14 ± 3.6	18 ± 7.2[b]
40	−2 ± 1.2	6 ± 3.7	9 ± 2.7	14 ± 3.5[b]	13 ± 3.0	14 ± 3.3[b]
50	−2 ± 1.7	4 ± 3.4	6 ± 2.3	14 ± 3.5[b]	14 ± 2.7	16 ± 2.9[b]
60	−2 ± 2.1	3 ± 3.6	4 ± 2.8	14 ± 3.5[b]	13 ± 2.7	14 ± 2.8[b]
80	−2 ± 1.7	2 ± 2.7	9 ± 2.7	17 ± 4.6[b]	13 ± 2.3	16 ± 4.3[b]
100	−1 ± 2.0	3 ± 3.6	8 ± 3.0	15 ± 3.2[b]	13 ± 2.1	19 ± 4.8[b]
120	−1.5 ± 2.0	5 ± 3.3	7 ± 3.1	15 ± 3.1[b]	13 ± 2.6	17 ± 2.9[b]

NZ, nonischemic myocardium; IZ, ischemic myocardium; group A, saline treated; group B, pranolium, 5 mg/kg bolus and 25 μg/kg/min infusion; group C, pranolium, 10 mg/kg bolus and 50 μg/kg/min infusion. Numbers in parentheses indicate number of experiments.

[a]Data are expressed as change in activation time, i.e., test-control (pretreatment).

[b]Significant differences from 0 min values are: $p < .05$.

decreases automaticity in the SA nodal tissue, the AV junction, and the ventricle. This action is a result of pranolium's ability to decrease the slope of spontaneous phase 4 depolarization. Finally, pranolium increases the ERP in both the atrioventricular conducting system and the canine ventricle. The relationship between these electrophysiologic actions and the antiarrhythmic actions of pranolium will be discussed in the following sections.

ANTIARRHYTHMIC ACTIVITY

Pranolium possesses antidysrhythmic properties in a number of experimental models of ventricular arrhythmias.

Ouabain-Induced Ventricular Tachyarrhythmias

One of the most widely used animal models for the determination of antiarrhythmic activity is that of the production of ventricular tachycardia in anesthetized dogs by the administration of ouabain (41). The criteria used to determine antiarrhythmic activity are: (a) reversion to normal sinus rhythm for a specified period of time, usually not less than 30 min; and (b) the failure of right vagal stimulation to expose automatic ectopic ventricular activity during sinus node arrest.

In a series of experiments performed in our laboratory, Schuster et al. (71) reported pranolium, given intravenously to dogs with ouabain-induced ventricular tachycardia, was successful in reestablishing normal sinus rhythm in doses of 2–3 mg/kg. Also, Patterson et al. (59), in a second series of experiments, found that

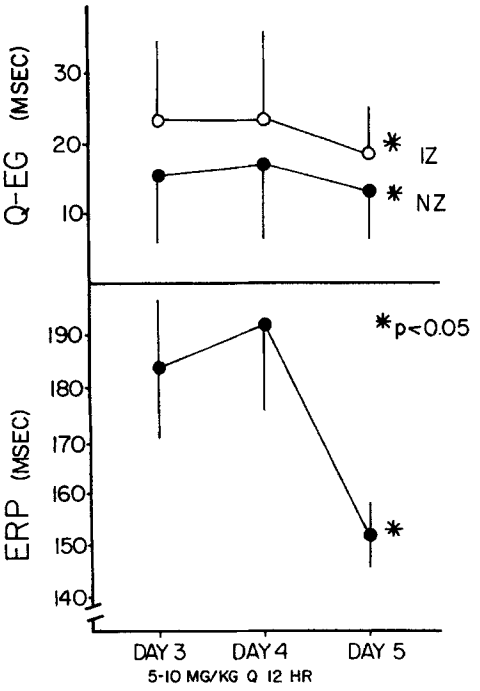

FIG. 8. Myocardial activation times and effective refractory periods. Myocardial activation times (Q-EG intervals) were measured for normal (NZ) and ischemic (IZ) myocardium both during (days 3 and 4) and after (day 5) chronic pranolium administration. Effective refractory periods (ERP) in normal myocardium were also measured. Data are expressed as means ± SD ($N = 8$). Pranolium administration increased myocardial activation times in both normal and ischemic myocardium ($p < 0.05$). Pranolium administration also produced an increase in ventricular refractoriness ($p < 0.05$). (From Patterson and Lucchesi, ref. 62, with permission.)

pranolium, when given *orally* in doses of 40 and 60 mg/kg to anesthetized dogs with ouabain-induced ventricular tachycardias, reestablished normal sinus rhythm within 64 ± 7 and 25 ± 9 min, respectively, after oral administration (Fig. 9).

Despite the ability of pranolium to slow conduction in ventricular myocardium and to increase refractoriness in AV nodal tissue, it appears to be an ideal drug for the treatment of arrhythmias resulting from digitalis toxicity. Thus, pranolium can be given safely in the presence of the digitalis glycosides, and concurrent administration of digitalis glycosides does not appear to be detrimental as far as impeding atrioventricular transmission.

Effects of Pranolium on Ventricular Automaticity After Experimentally Induced Myocardial Infarction

Another method of determining the antiarrhythmic efficacy of a drug is by administering the agent to a conscious dog prepared by the method of Harris (21). Schuster et al. (71) reported that in dogs studied 48 hr after a two-step ligation of LAD, each animal exhibited spontaneous ventricular arrhythmias in which an average of 76.3% of the total number of heart beats (102.7 ± 13.9 out of 135.1 ± 9.9 beats/min) originated from ventricular foci. Pranolium, in an average dose of 5.7 mg/kg (2.5–10 mg/kg) significantly reduced the ectopic heart rate to 16.0 ± 10.7 beats/min (14.5% of ventricular rate) (Figs. 10 and 11). The antiarrhythmic action

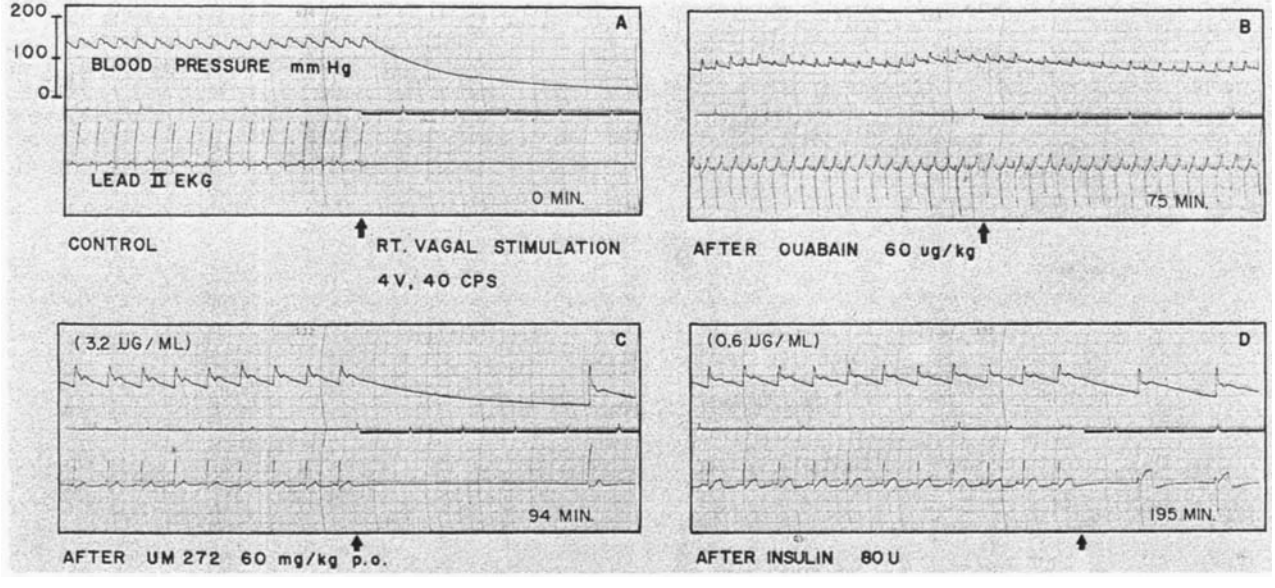

FIG. 9. Reversal of ouabain arrhythmia after oral UM-272. Blood pressure and electrocardiographic recordings. Panel **A** shows arterial pressure and lead II ECG before pharmacologic intervention. Right vagus nerve stimulation produces sinus arrest. Panel **B** was recorded after administration of ouabain, 60 μg/kg, and immediately before pranolium administration (75 min after start of experiment). Vagus nerve stimulation produced no change in ventricular rate. Panel **C** was recorded 19 min after p.o. pranolium administration, 60 mg/kg. No ectopic beats were present during vagally induced sinus arrest. Panel **D** was recorded 2 hr after pranolium administration. (From Schuster et al., ref. 71, with permission.)

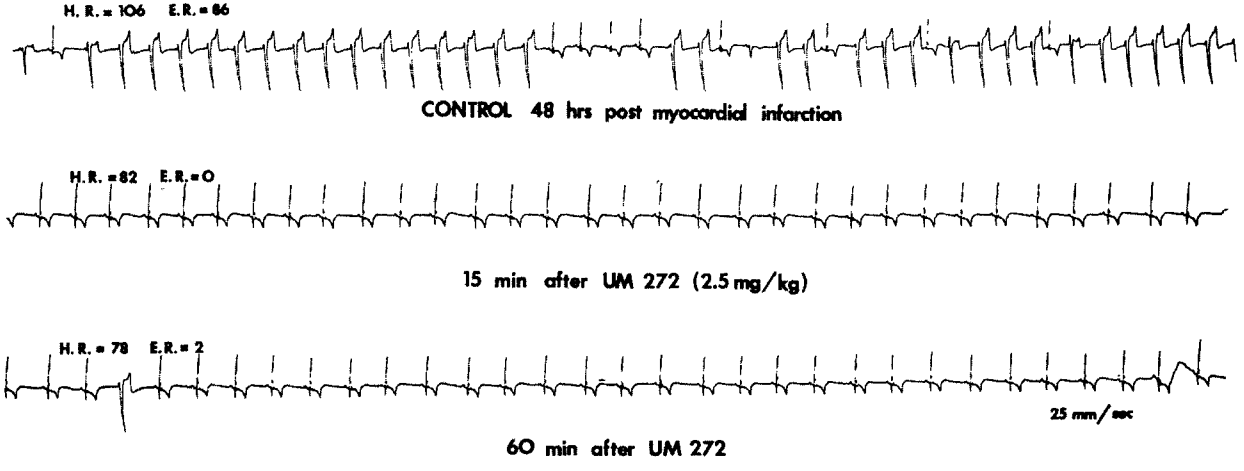

FIG. 10. The effect of pranolium (UM-272, 2.5 mg/kg i.v.) on the spontaneous ventricular tachycardia in the awake dog 48 hr after a two-stage ligation of the anterior descending coronary artery (Harris procedure). Each panel shows the lead II ECG. The numbers above the electrocardiographic tracing indicate the heart rate (H.R.) and the ectopic rate (E.R.). The administration of pranolium abolished the ventricular ectopic rhythm and restored normal sinus rhythm that was still present 60 min later, as shown in the last segment. (From Schuster et al., ref 71, with permission.)

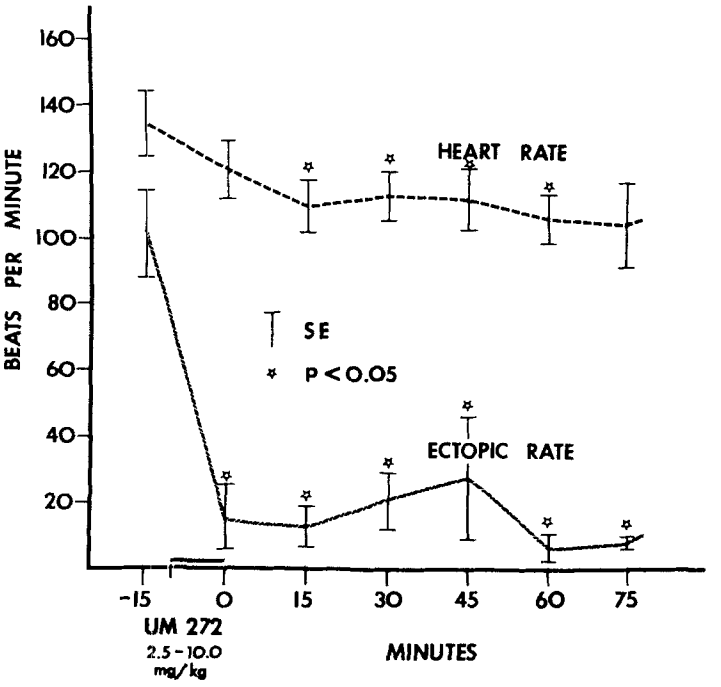

FIG. 11. The effect of pranolium in 7 conscious dogs 48 hr after experimentally induced myocardial infarction. Each animal was studied during the phase of spontaneous ventricular tachycardia and received an intravenous infusion of pranolium until sinus rhythm was restored. Ectopic beats were defined as those beats not of sinoatrial origin. (From Schuster et al., ref. 71, with permission.)

of pranolium persisted in 6 of 7 animals for at least 1 hr. In 2 animals, the electrocardiogram was monitored for 2 hr with no significant increase in ectopic rate observed.

Although ouabain-induced ventricular arrhythmias and ventricular tachyarrhythmias present 24–72 hr after experimental myocardial infarction are commonly used to evaluate antiarrhythmic drugs, these models poorly simulate the basis for ventricular arrhythmias in man. Both cardiac glycoside-induced ventricular arrhythmias and ventricular arrhythmias present 24–72 hr after myocardial infarction result from altered Purkinje fiber automaticity (24,37). Enhanced automaticity of damaged myocardial tissue may play a role in some arrhythmias. However, it has been suggested that most ventricular arrhythmias associated with myocardial ischemia and infarction in man probably result from localized reentry of myocardial electrical activity (10,24,37). Accurate evaluation of antiarrhythmic activity of drugs requires animal models that more closely simulate the clinical situation in man.

The presence of reentrant ventricular arrhythmias, particularly complex ventricular arrhythmias such as multiform premature ventricular beats, coupled extrasystoles, and ventricular tachycardia (Lown grades 3–5), in patients with coronary

artery disease is a major risk factor associated with the future development of ventricular fibrillation (68,72,80). Prevention of ventricular fibrillation appears to be associated with suppression of the continuous underlying myocardial electrical instability responsible for the development of ventricular tachyarrhythmias and ventricular fibrillation rather than with an overall reduction in the number of premature ventricular beats (26,50,51). Prevention of reentrant ventricular arrhythmias and ventricular fibrillation may be dependent upon the ability of the drug to affect the underlying substrate, the antifibrillatory properties of the drug, rather than upon the ability to suppress premature ventricular beats, the antiarrhythmic properties of the drug. Therefore, the following animal models were used to evaluate the antifibrillatory properties of pranolium.

Reentrant Ventricular Arrhythmias Resulting from Acute Coronary Artery Occlusion

Schuster et al. (71) studied the ability of pranolium to prevent the development of ventricular fibrillation resulting from repeated occlusions of the LAD coronary artery in the anesthetized dog. Each occlusion lasted 10 min and was followed by reperfusion. In control animals, 11 of 15 animals fibrillated after one, two, or three occlusions. In the pranolium-treated group (10 mg/kg, i.v.), only 5 of 15 animals developed ventricular fibrillation ($p < 0.025$) (71).

In a second series of experiments in which occlusion of the anterior descending coronary artery was maintained for 20 min, 10 out of 10 untreated animals developed ventricular fibrillation upon occlusion or upon reperfusion. In the pranolium-treated group, none of the animals fibrillated during the occlusion and 4 of 10 fibrillated upon restoration of coronary artery blood flow. The difference between control and drug-treated groups proved significant ($p < 0.05$) (71).

Ventricular Fibrillation Threshold Determination

In unpublished experiments from our laboratory, Kniffen (32) showed that pranolium was effective in elevating the ventricular fibrillation threshold (the lowest current intensity producing sustained ventricular fibrillation) in the anesthetized dog. In these experiments the sinus node was crushed and the ventricular rate maintained by electrical pacing at a frequency of 2 Hz. A train of 60-Hz pulses (350 msec in duration) was synchronized to the ventricular pacing stimulus and was delivered after every sixth driven beat.

Control measurements of fibrillation threshold were 5.4 ± 0.38 mA (X ± SEM). After a temporary 2-min occlusion of a branch of the anterior descending coronary artery, the fibrillation threshold was reduced to 2.4 ± 0.2 mA. Administration of pranolium (5 mg/kg) increased the control values to 11.5 ± 1.9 mA at 30 min after drug ($p < 0.01$). As seen in Fig. 12, pranolium administration also significantly increased ventricular fibrillation thresholds determined in the presence of regional myocardial ischemia (6.7 ± 0.18 mA versus 2.4 ± 0.2 mA predrug) ($p < 0.05$).

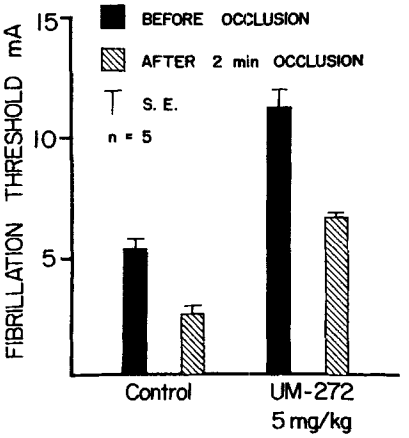

FIG. 12. Ventricular fibrillation threshold determinations. Gated trains (60 Hz, 350 msec train duration) of 4-msec pulses were introduced into the right ventricle. Pranolium (5 mg/kg) significantly increased the current intensity needed to produce ventricular fibrillation. (From Kniffen, ref. 32, with permission.)

Reentrant Ventricular Arrhythmias Produced by Programmed Electrical Stimulation in Conscious and Anesthetized Dogs

Recently, the technique of programmed electrical stimulation (PES) has been used to expose the underlying myocardial substrate responsible for recurrent ventricular tachyarrhythmias (including ventricular fibrillation) in patients exhibiting these arrhythmias spontaneously (27–29,79). Exposure of the arrhythmia with this technique (involving the transvenous or transarterial placement of electrocatheters in either right or left ventricle followed by insertion of 1, 2, or 3 premature ventricular beats during atrial or ventricular pacing) allows the serial testing of a number of antiarrhythmic drugs to determine which dose of which particular agent best suppresses the arrhythmia. This technique has also lent itself to the examination of antiarrhythmic agents in the experimental animal (17,46,58,60,62,63). Gibson and Lucchesi (17) examined the effect of pranolium in anesthetized dogs which had previously undergone experimentally induced myocardial infarction. The dogs were instrumented with a bipolar plunge electrode inserted into the septum, an atrial pacing electrode, and bipolar composite electrodes in which one composite electrode was placed over the ischemic injured myocardium and the other electrode placed over adjacent normal ventricular myocardium (Fig. 13). Before pranolium administration, premature ventricular stimuli delivered to the bipolar septal electrode elicited nonsustained ventricular tachycardia in 3 animals, sustained ventricular tachycardia in 2 animals, and ventricular fibrillation in 3 animals. In each animal, these arrhythmias were associated with depressed, delayed cardiac conduction through injured myocardium. The injured zone electrocardiogram recorded from the bipolar composite electrode fractionated into a continuous series of asynchronous spikes which bridged the entire diastolic interval between consecutive beats (Figs. 14 and 15). Thirty minutes after intravenous pranolium (5 mg/kg), PES produced nonsustained ventricular tachycardia in 2 animals. Ventricular arrhythmias were not induced in the remaining animals. The cycle length of ventricular tachycardia after

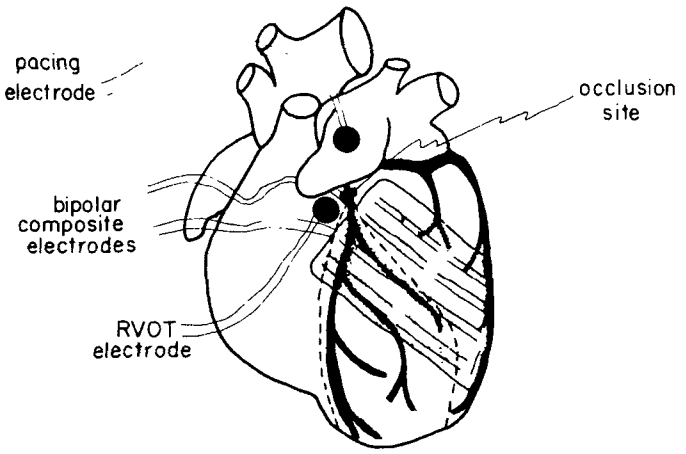

FIG. 13. Instrumentation for programmed electrical stimulation. A bipolar electrode was sewn to the left atrial appendage to enable control of ventricular rate via atrial pacing. A plunge bipolar electrode was placed into the interventricular septum adjacent to the right ventricular outflow tract. Composite bipolar electrodes were placed on normal and ischemically injured left ventricular myocardium.

pranolium (345 ± 5 msec) was significantly increased compared with predrug values (187 ± 16 msec) ($p < 0.05$). The antiarrhythmic action of pranolium was maintained in excess of 2 hr after intravenous dosing.

In each experiment, pranolium progressively depressed the amplitude and duration of the ischemic fragmented deflection recorded from the injured zone electrogram during the ventricular beats, although having no effect on the discrete potentials recorded from the adjacent normal zone. Before pranolium, the injured-zone potentials persisted for 169 ± 18 msec and thus bridged the diastolic interval. The duration of the diastolic electrical potentials was reduced to 110 ± 22 msec ($p < 0.05$) 30 min after pranolium (17). This action probably results from the ability of pranolium to slow conduction preferentially in injured myocardium, an action previously demonstrated in acutely ischemic ventricular myocardium (15). Conduction in the most severely depressed and delayed areas may be further depressed by pranolium so that conduction block occurs in the injured myocardium. This is supported by the observation that the cycle length of the tachycardia increased after pranolium. This suggests that impairment of already depressed cardiac conduction and prolonged refractoriness of different segments of a reentrant pathway are involved in the antiarrhythmic actions of pranolium and that these electrophysiologic effects may result in an antifibrillatory action.

Chronic Administration of Pranolium in the Conscious Dog

Patterson and Lucchesi (62) examined the actions of pranolium in conscious dogs that had previously been subjected to myocardial infarction and instrumented as described previously, and then subjected to PES beginning 3 days post-myocardial infarction.

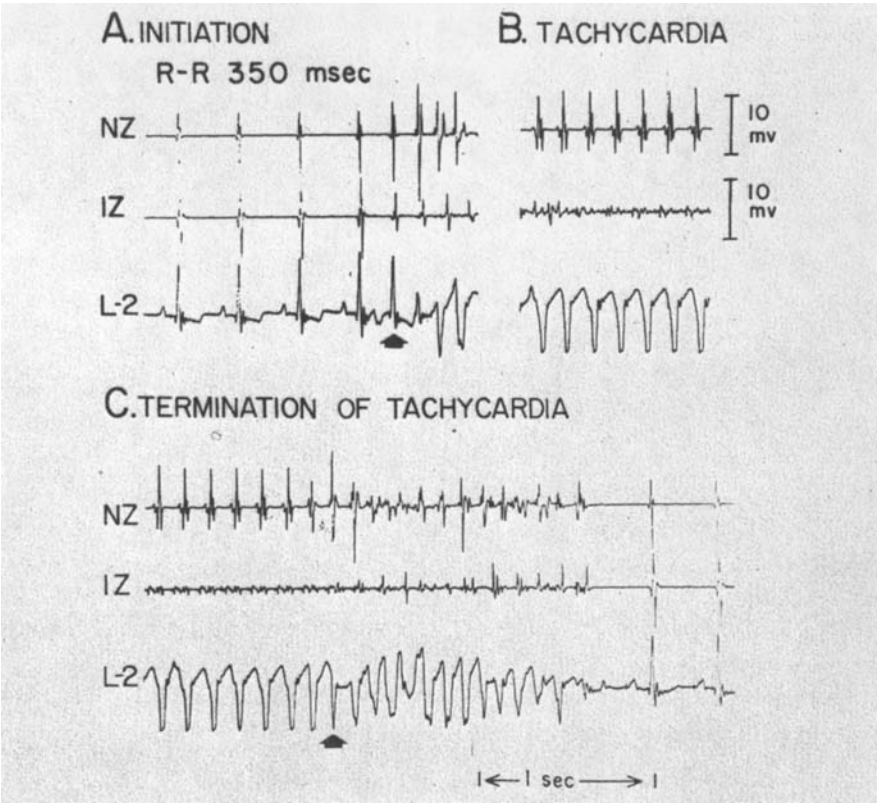

FIG. 14. Initiation and termination of sustained ventricular tachycardia by premature stimuli. NZ, composite electrogram from normal myocardium; IZ, composite electrogram from injured myocardium; L-2, lead II ECG. In panel **A**, a premature beat *(arrowhead)* produced ventricular tachycardia. Panel **B**, uniform ventricular tachycardia is seen. The epicardial activity of the injured zone *(middle trace)* is fragmented and asynchronous, whereas that of the normal zone *(upper trace)* remains synchronous and discrete. Panel **C**, a burst of ventricular pacing *(arrowhead)* is used to terminate the tachycardia. (From Gibson and Lucchesi, ref. 17, with permission.)

Pranolium (5 or 10 mg/kg) was administered intravenously every 12 hr beginning 24 hr before PES on day 3 and continued through 12 hr prior to PES on day 4. PES was performed 12 hr after the last dose of pranolium on days 3 and 4, 30 min after acute pranolium administration on day 3, and 36 hr after the last dose of pranolium on day 5. Twenty dogs served as saline-treated controls and underwent PES on days 3 and 4 after myocardial infarction.

The results of PES in saline- and pranolium-treated animals are shown in Fig. 16. Ventricular tachyarrhythmias were induced by PES in all 20 control animals on days 3, 4, and 5 after myocardial infarction. Sustained ventricular tachycardias had a cycle length of 186 ± 31 msec. Self-terminating ventricular tachycardias (nonsustained ventricular tachycardia) were 18 ± 7 beats in duration with a cycle length of 169 ± 13 msec. In pranolium-treated animals, PES performed 12 hr after the last pranolium dose produced nonsustained ventricular tachycardia in 2 animals

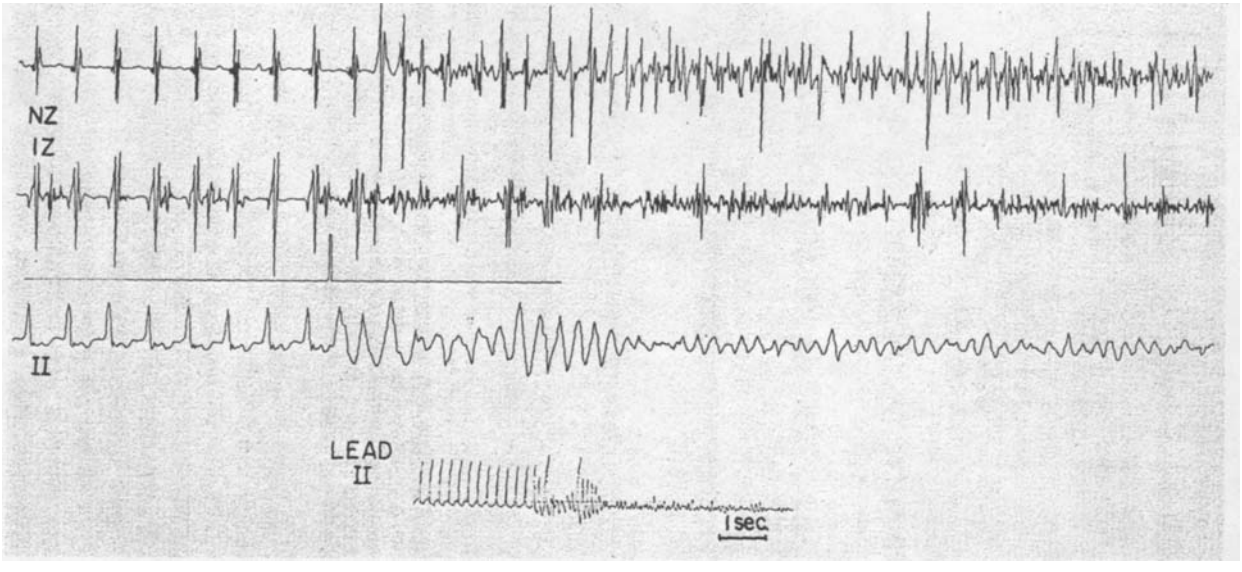

FIG. 15. Composite electrograms from normal (NZ) and ischemically injured (IZ) left ventricular myocardium, and a lead II ECG are shown from an animal on day 4 after myocardial infarction. The introduction of a single premature ventricular stimulus produces ventricular fibrillation. (From Gibson and Lucchesi, ref. 17, with permission.)

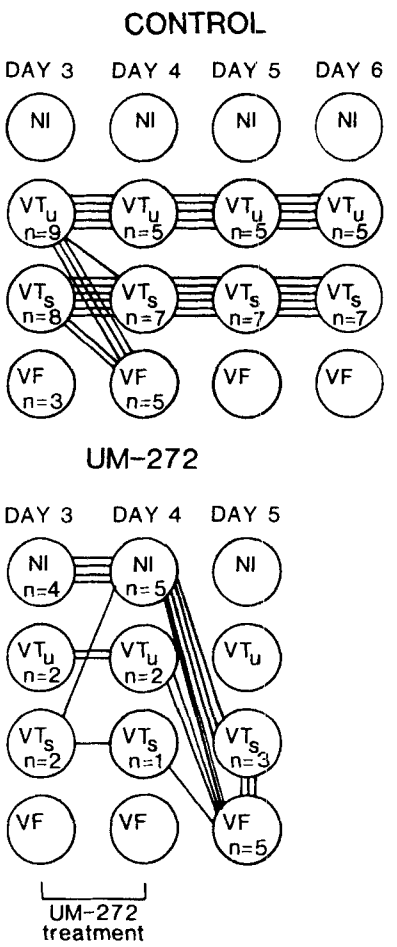

FIG. 16. Effect of pranolium (UM-272) on inducible ventricular reentrant arrhythmias in the conscious dog. Note that the termination of pranolium treatment caused an exacerbation of arrhythmias in all dogs. NI, noninducible; VT_u, nonsustained ventricular tachycardia; VT_s, sustained ventricular tachycardia; VF, ventricular fibrillation. The number of animals *(n)* is included in each ball.

(cycle length, 296 and 316 msec) and sustained ventricular tachycardia in 2 animals (cycle length, 304 and 320 msec) on day 3. The duration of nonsustained ventricular tachycardia was 4.2 ± 1.6 beats. If ventricular tachycardia could not be induced with PES at two times diastolic threshold ($N = 4$), PES at five times diastolic threshold was performed, resulting in nonsustained ventricular tachycardia (3.6 ± 1.2 beats) in 2 animals.

Thirty minutes after the acute administration of the third dose of pranolium on day 3, ventricular tachyarrhythmias could not be induced in 7 of 8 animals with PES at two or five times diastolic threshold. In the remaining animal, the cycle length of the sustained ventricular tachycardia had increased from 324 to 345 msec.

On day 4 after myocardial infarction, PES in pranolium-treated animals at two times diastolic threshold failed to elicit ventricular tachycardia in 5 animals. Nonsustained ventricular tachycardia (cycle length, 284 and 312 msec) was produced

in 2 animals and sustained ventricular tachycardia (cycle length, 320 msec) in 1 animal. PES at five times diastolic threshold produced nonsustained ventricular tachycardia in 1 of 5 noninducible animals.

On day 5 after myocardial infarction, 36 hr after withdrawal of pranolium, PES produced ventricular fibrillation in 5 animals and sustained ventricular tachycardia in 3 dogs. The sustained ventricular tachycardias were rapid (132 ± 19 msec cycle length) and degenerated to ventricular fibrillation in all 3 animals.

Administration of pranolium raised the ventricular refractory period to 183 ± 12 msec on day 3 and 191 ± 18 msec on day 4. The effective refractory period of the normal left ventricle on day 5, after withdrawal of pranolium, was 152 ± 5 msec ($p < 0.05$ versus day 3 or day 4). An example of PES in a pranolium-treated animal on days 3–5 after myocardial infarction is shown in Fig. 17. This study demonstrates pranolium's ability to inhibit inducible cardiac tachyarrhythmias.

Conscious Canine Model of Sudden Coronary Death

Animal models used to evaluate the antiarrhythmic efficacy on potential therapeutic agents do not mimic the myocardial electrical instability and spontaneous occurrence of ventricular fibrillation associated with the development of sudden coronary death in man. The following canine model (61) of sudden coronary death has been developed recently in our laboratory and may provide a model that closely resembles the clinical situation in man in that ventricular fibrillation occurs spontaneously in response to regional myocardial ischemia.

Male mongrel dogs are anesthetized and myocardial ischemic injury is produced within the distribution of the left anterior descending coronary artery by temporary occlusion of the vessel (90 min) followed by reperfusion in the presence of a critical stenosis. The left circumflex coronary artery is isolated and the tip of a 30-gauge insulated silver wire is inserted into the vessel lumen (66). A plunge bipolar electrode is placed in the interventricular septum. Subcutaneous electrodes are implanted for electrocardiographic monitoring and the chest closed in layers.

At day 3 after myocardial infarction, the animals were randomly assigned to treatment groups. The first group received saline and the second group received pranolium, 5 mg/kg i.v., every 6 hr. At 24 hr after initiation of drug therapy, PES was performed. The next drug dosage was administered and a current of 150 μA was applied to the intimal surface of the left circumflex coronary artery. A 9-volt battery, potentiometer, and biotelemetry transmitter were self-contained within the pouch of a nylon vest, thus allowing the animal free movement within a limited area. The lead II electrocardiogram was recorded continuously and stored on magnetic tape. The current flow to the intimal surface of the LCX coronary artery was maintained for 12 hr.

Administration of pranolium prevented the induction of ventricular tachycardia by PES. No sustained ventricular arrhythmias were produced in 9 animals while nonsustained ventricular tachycardia was produced in the 1 remaining animal. In control animals, PES produced nonsustained ventricular tachycardia in 7 animals,

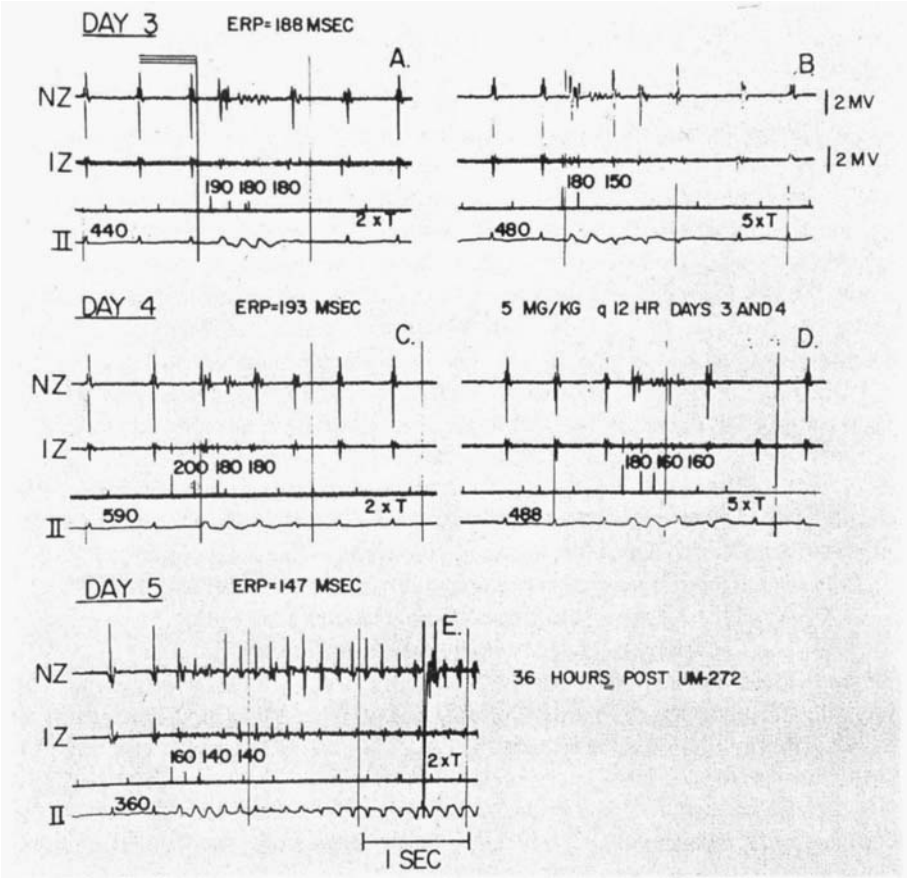

FIG. 17. Prevention of reentrant ventricular arrhythmias by pranolium (UM-272). Normal zone (NZ) and ischemic zone (IZ) bipolar composite electrograms, and a lead II ECG (II) are shown for serial studies on a representative pranolium-treated animal. Sinus cycle lengths (msec) are given in the lower left of each panel. **A:** Three days after myocardial infarction and during pranolium treatment (5 mg/kg every 12 hr), three premature ventricular stimuli with coupling intervals of 190, 180, and 180 msec failed to produce reentrant cardiac arrhythmias. **B:** The stimulus strength was raised to five times diastolic threshold, enabling shorter coupling intervals. Two premature ventricular stimuli at coupling intervals of 180 and 150 msec produced a slow three-beat tachycardia. Pranolium treatment was continued through day 4 after myocardial infarction (panels **C** and **D**). **C:** Three premature ventricular stimuli at coupling intervals of 200, 180, and 180 msec failed to produce ventricular tachycardia. When an increase in stimulus strength to five times diastolic threshold enabled earlier coupling intervals to be obtained [180, 160, and 160 msec **(D)**], three premature stimuli still failed to produce ventricular tachycardia. On day 5 after myocardial infarction, 36 hr after the last dose of pranolium three premature beats at two times diastolic threshold with coupling intervals of 160, 140, and 140 msec produced a polymorphic ventricular tachycardia which degenerated to ventricular fibrillation. (From Patterson and Lucchesi, ref. 62, with permission.)

sustained ventricular tachycardia in 2 animals, and no ventricular arrhythmias in 1 animal.

Current application to the intimal surface of the coronary artery produced denuding of the intimal surface and exposure of underlying collagen (66). Platelet aggregates and a platelet thrombus form, resulting in partial and, finally, complete occlusion of the vessel lumen. In saline-treated animals, ST-segment depression or elevation in excess of 0.3 mV developed at 99 ± 106 min (X ± SD) after initiation of current flow to the intimal surface of the left circumflex coronary artery. Premature ventricular contractions developed at 111 ± 108 min followed by ventricular tachycardia at 131 ± 118 min. Ventricular fibrillation developed in all 10 saline-treated animals at 173 ± 143 min. An example is shown in Fig. 18.

Pranolium significantly reduced the incidence of ventricular fibrillation produced by acute myocardial ischemia within the left circumflex coronary arterial bed in the presence of left anterior descending myocardial infarction. Four of 10 animals survived for 24 hr after initiation of current flow to the intimal surface of the left circumflex coronary artery ($p < 0.05$). However, the drug did not prevent coronary artery thrombosis and myocardial ischemia. ST-segment changes appeared at 156 ± 89 min followed by the development of premature ventricular contractions at 168 ± 93 min. An example of a pranolium-treated animal is shown in Fig. 19. Survival curves for saline- and pranolium-treated animals are shown in Fig. 20.

No differences were seen in myocardial infarct masses in the left anterior descending coronary artery distribution of saline- (19 ± 9% of total left ventricular mass) and pranolium-treated groups (19 ± 13% of total left ventricular mass). In pranolium-treated animals surviving for 24 hr ($N = 4$), myocardial infarction (17 ± 10% of total left ventricular mass) was present also in the left circumflex coronary artery distribution. Only left anterior descending myocardial infarction was observed in animals developing ventricular fibrillation. No evidence of ischemic injury was observed in the myocardial distribution of the left circumflex bed due to the rapid development of ventricular fibrillation in response to regional ischemia in the region of the LCX coronary artery. Thrombus mass, within the left circumflex coronary artery, was not significantly different between saline- (8 ± 7 mg) and pranolium-treated (14 ± 14 mg) groups.

The beneficial action of pranolium in preventing the induction of reentrant ventricular tachyarrhythmias and reducing the frequency of spontaneous development of ventricular fibrillation may be a result of the drug's ability to depress myocardial conduction or increase myocardial refractoriness. As seen in the studies conducted in the anesthetized dog, pranolium depressed conduction in ischemically injured tissue to the extent that conduction failed where it was most severely depressed. Failure to conduct in these depressed regions resulted in failure of the premature beats to initiate reentrant arrhythmias (17).

The increase in the refractory period of normal myocardium observed after chronic pranolium treatment in the conscious dog (62) is similar in magnitude to that observed with bretylium and other class III antiarrhythmic drugs. Augmentation of refractoriness in normal myocardium may prevent the induction of ventricular tach-

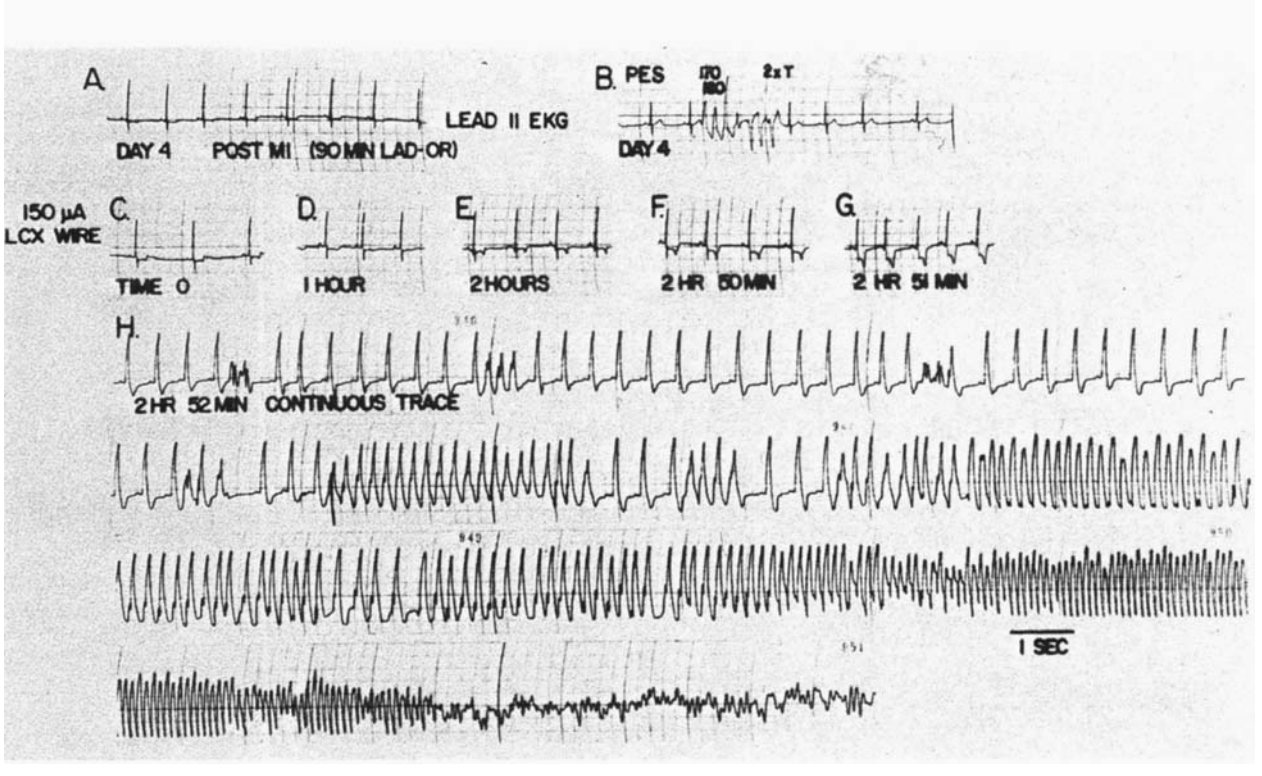

FIG. 18. Ventricular fibrillation in a conscious canine model of sudden coronary death. In panel **A**, normal sinus rhythm is present on day 4 after myocardial infarction. Two premature ventricular stimuli introduced at coupling intervals of 170 and 180 msec produce a nonsustained ventricular tachycardia. In panel **C**, a current of 150 μA is applied to the intimal surface of the LCX coronary artery of the conscious dog. Panels **D** and **E** show normal sinus rhythm at 1 and 2 hr after the initiation of current flow to the LCX coronary artery. At 2 hr and 50 min (panel **F**) and 2 hr and 51 min (panel **G**), ST-segment depression is present. At 2 hr and 52 min, premature ventricular contractions and nonsustained ventricular tachycardia develop, with the ventricular rhythm degrading to ventricular fibrillation.

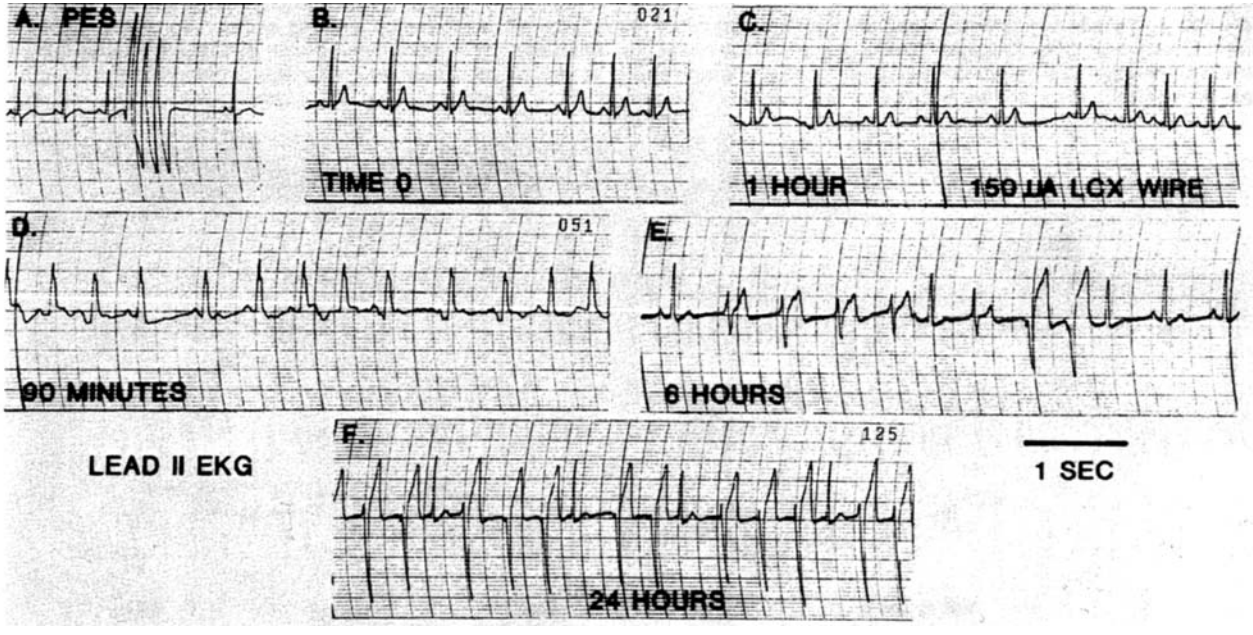

FIG. 19. Protection from ventricular fibrillation by UM-272 in a conscious canine model of sudden coronary death. Electrocardiographic recordings. In panel **A**, 6 hr after the last pranolium dose (5 mg/kg i.v., three previous doses), programmed electrical stimulation (PES) fails to produce ventricular tachycardia. In panel **B**, a current of 150 μA is then applied to the intimal surface of the left circumflex coronary artery. In panel **C**, 1 hr later, normal sinus rhythm is still present. At 90 min (panel **D**), acute myocardial ischemia is present. Panels **E and F** show the later development of premature ventricular contractions as myocardial infarction develops.

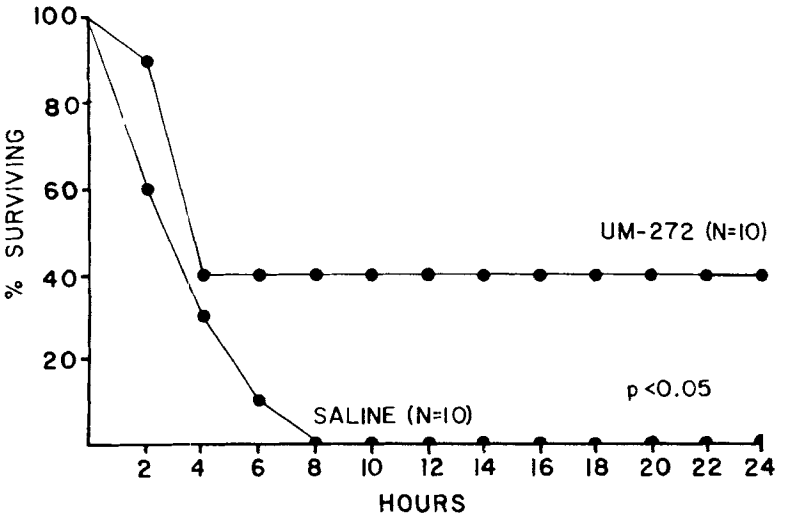

FIG. 20. The effect of pranolium (UM-272) upon survival in a canine model of sudden coronary death. Pranolium significantly increased ($p < 0.05$) survival at 24 hr.

yarrhythmias by preventing premature beats from occurring at cycle lengths sufficiently early to establish a reentrant pathway. Alternatively, fractionation and prolongation of electrical activity within the ischemically injured zone produced by premature stimuli may fail to excite surrounding normal myocardium when refractoriness of the tissue exceeds the duration of electrical activity within the ischemically injured zone.

Antiarrhythmic Activity in Man

A study by Reele et al. (65) evaluated the actions of intravenous pranolium in patients with ventricular arrhythmias. Pranolium, 10 mg/kg, given over a period of 100 min, significantly reduced the number and complexity of ventricular arrhythmias. This action was obtained without significant hemodynamic or systemic toxicity. However, further studies will be needed to establish efficacy and safety of pranolium in man.

HEMODYNAMICS

Beta-Blockade

The lack of significant beta-adrenergic receptor blocking activity by pranolium was demonstrated by Schuster et al. (71). In the isolated rabbit right atrial strip preparation (Fig. 21), the cumulative dose response to the chronotropic effects of isoproterenol was studied in the presence and absence of pranolium. At a concentration of 10^{-6} M pranolium produced no significant shift in the isoproterenol concentration-response curve. However, at a concentration of 10^{-4} M, pranolium

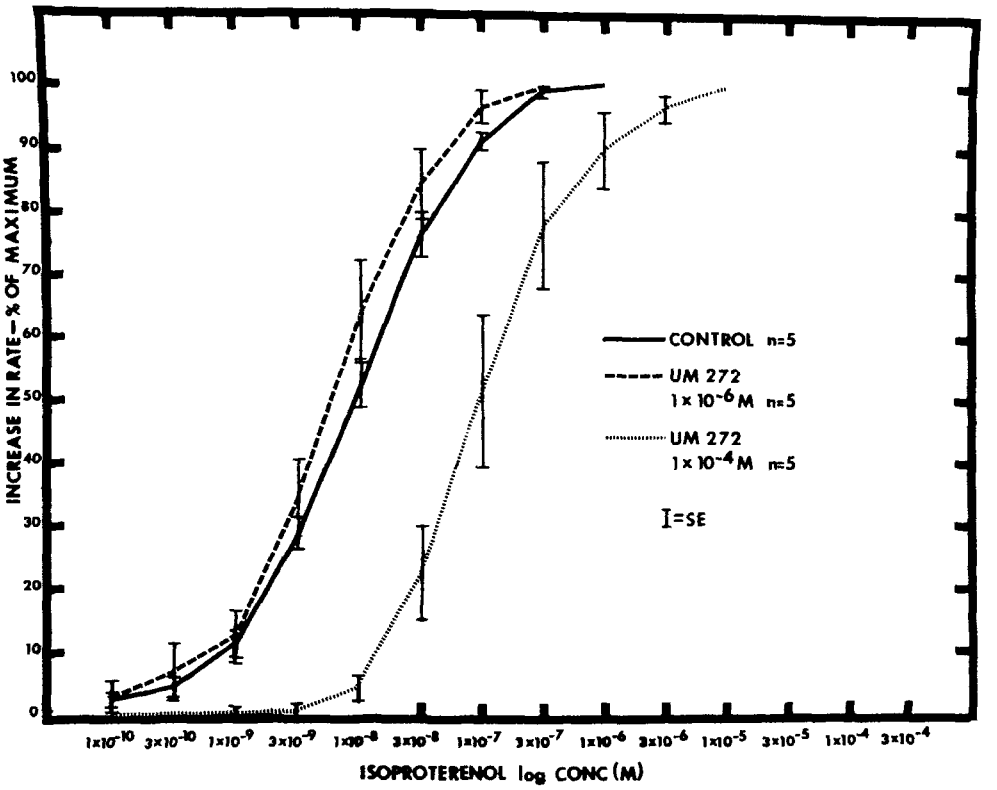

FIG. 21. Effects of pranolium (UM-272) on the chronotropic concentration-effect curves for isoproterenol upon isolated right atrial strips. The cumulative log-concentration-effect curves for isoproterenol were determined in three separate groups—a control group and two groups in which the isoproterenol concentration-effect curves were determined 60 min after the addition of 10^{-6} and 10^{-4} M pranolium. Only at 10^{-4} M did pranolium cause a statistically significant shift to the right in the concentration-effect curve ($p < .01$). (From Schuster et al., ref. 71, with permission.)

produced a statistically significant shift to the right. In addition, both the inotropic and chronotropic responses to increasing doses of isoproterenol were studied before and after pranolium in open-chest anesthetized dogs (Table 6). The increase in both force and rate seen in response to isoproterenol alone did not differ significantly from that seen after 0.5, 4, or 10 mg/kg of pranolium. When a separate group of dogs was studied after receiving 0.5 mg/kg propranolol, there was a prominent shift to the right of the dose-response relationship to isoproterenol. Thus, pranolium does not exhibit significant beta-adrenergic receptor blocking activity in the anesthetized open-chest dog and only a minimal degree of beta-adrenergic receptor blockade at a high concentration in the isolated rabbit right atrial strip.

The isolated calf tracheal muscle brought to submaximal contraction with acetyl-β-methylcholine shows prominent relaxation in the presence of beta-adrenergic

TABLE 6. *Effects of pranolium and propranolol upon isoproterenol-induced chronotropic and inotropic responses*

Dose of isoproterenol (μg/kg)	Mean increase in heart rate			Mean increase in force		
	Before (beats/min)	After (beats/min)	*p*	Before (g)	After (g)	*p*
		Pranolium, 0.5 mg/kg (*N* = 5)				
0.05	3.6 ± 0.8	4.2 ± 1.4	>.05	7.4 ± 1.3	7.2 ± 1.8	>.05
0.10	8.9 ± 1.5	5.4 ± 4.2	>.05	17.6 ± 3.3	13.4 ± 1.5	>.05
0.20	16.0 ± 3.1	13.0 ± 3.5	>.05	30.4 ± 4.5	31.0 ± 4.5	>.05
0.40	28.6 ± 3.8	27.0 ± 4.6	>.05	54.4 ± 17.0	59.6 ± 8.3	>.05
0.80	46.0 ± 4.4	41.0 ± 6.2	>.05	84.0 ± 12.5	94.2 ± 7.3	>.05
		Propranolol, 0.5 mg/kg (*N* = 5)				
0.05	4.4 ± 1.9	0.0 ± 0.0	<.10	8.0 ± 1.4	0.0 ± 0.0	<.005
0.10	7.6 ± 2.1	0.2 ± 0.2	<.025	16.2 ± 2.1	0.2 ± 0.2	<.005
0.20	12.4 ± 2.9	2.6 ± 0.9	<.025	38.0 ± 5.9	1.9 ± 0.4	<.005
0.40	26.0 ± 5.4	3.0 ± 0.9	<.010	65.9 ± 7.8	4.8 ± 0.6	<.005
0.80	59.2 ± 21.4	7.0 ± 1.4	<.005	95.4 ± 12.5	11.8 ± 1.7	<.005
1.6		23.8 ± 10.7			23.4 ± 3.2	
3.2		27.0 ± 6.1			46.8 ± 6.2	
6.4		47.8 ± 8.5			88.2 ± 11.4	
		Pranolium, 4.0 mg/kg (*N* = 5)				
0.05	5.2 ± 0.7	3.2 ± 0.9	>.05	11.4 ± 1.9	7.6 ± 1.2	>.05
0.10	9.2 ± 1.9	5.2 ± 1.3	>.05	27.2 ± 3.6	19.2 ± 3.3	>.05
0.20	18.0 ± 4.7	13.2 ± 2.6	>.05	54.2 ± 6.3	46.0 ± 7.0	>.05
0.40	32.8 ± 4.7	24.2 ± 5.4	>.05	91.6 ± 13.9	86.0 ± 10.9	>.05
0.80	53.4 ± 6.0	38.8 ± 6.6	>.05	137.2 ± 17.4	139.4 ± 16.8	>.05
		Pranolium, 10 mg/kg (*N* = 5)				
0.025	7.8 ± 1.6	6.6 ± 1.7	>.4	29.4 ± 3.9	26.8 ± 4.3	>.4
0.050	14.4 ± 2.0	15.6 ± 3.8	>.5	52.8 ± 6.2	62.4 ± 7.4	>.2
0.100	27.2 ± 3.7	28.8 ± 5.3	>.5	76.4 ± 7.2	93.4 ± 8.5	>.1
0.200	44.6 ± 7.6	45.6 ± 8.2	>.5	88.0 ± 8.7	123.6 ± 11.9	<.025
0.400	59.0 ± 10.2	62.0 ± 10.2	>.5	94.0 ± 10.4	135.5 ± 12.4	<.025

Force and heart rate were measured as increase from control. The values are the means ± SE obtained from 4 groups of 5 dogs each. Data analyzed by self-paired analysis. The drug was administered intravenously.

agonists. The cumulative dose-response curve for the beta-adrenergic agonist isoproterenol, in this system, in the presence of increasing concentrations of propranolol shows a parallel shift to the right, characteristic of competitive antagonism. Pranolium, in the same concentrations as propranolol (10^{-7}–10^{-5} M) fails to shift the cumulative dose-response curve to the right, thus showing a lack of competitive antagonism to isoproterenol at the beta-adrenergic receptor (5).

Heart Rate, Blood Pressure, and Cardiac Output

Pranolium significantly reduces heart rate, cardiac output (87), and blood pressure in anesthetized dogs (57). A decrease in heart rate and cardiac output was seen with an increasing cumulative dose (1 to 3 mg/kg). Systolic pressure, however, did not exhibit the same dose-response relationship. Single 3-mg/kg doses of pranolium produced a significant decrease in heart rate and cardiac output but a significant change in systolic pressure was not seen.

Other investigators showed a significant decrease in heart rate after 5 mg/kg pranolium in anesthetized, open-chest dogs. Cardiac output and mean blood pressure were not significantly altered (40).

O_2 Consumption

Since mammalian myocardium relies largely on aerobic metabolism for its energy requirements, the oxygen supply and demand ratio is crucial. The two major ways to increase this ratio are to increase myocardial oxygenation and/or decrease myocardial oxygen demand (56). Since the oxygen content of blood is fairly constant, the best way to increase myocardial oxygenation is to increase coronary blood flow through dilation of the coronary arteries. In hearts with coronary artery disease, the ability to increase flow is severely limited (11). A possible therapeutic approach, then, is to decrease myocardial oxygen demand (45).

Possible pharmacologic interventions include the use of beta-adrenergic receptor blocking agents, such as propranolol, to decrease myocardial oxygen requirements (74). The use of such beta-adrenergic receptor blocking drugs, however, may aggravate many cardiac disease states by removing essential sympathetic compensation (6,76), especially in the failed heart.

Pranolium decreases myocardial oxygen consumption in both the open-chest (33) or closed-chest (57,87) anesthetized dog and in the isolated perfused heart *in situ* (33,82). Pranolium, 10 mg/kg, has been shown to decrease myocardial oxygen consumption in anesthetized, open-chest dogs (Fig. 22) with only minimal changes in cardiac force and heart rate (33). In the closed-chest anesthetized dog (57) pranolium decreases myocardial oxygen consumption by decreasing heart rate and force, which also results in a decrease in cardiac output and tension-time index. In isolated, blood perfused canine hearts (Fig. 23) with a constant afterload, controlled ventricular volume, and lack of sympathetic reflexes, pranolium produces negative inotropic and a negative chronotropic effect which are associated with the decrease in oxygen consumption. When heart rate in this preparation is returned to predrug levels, however, myocardial oxygen consumption also returns towards control, indicating that it is the decrease in rate that is primarily responsible for the decrease in MVO_2.

In the isolated blood-perfused canine heart, with constant coronary blood flow (82), intracoronary infusion of pranolium produces a significant decrease in MVO_2 at 1.3, 2.5, and 5.0 mg/min for 25 min, but not at 0.3 mg/min for 15 min. Infusions of pranolium in a dose of 2 mg/min $\times$ 15 min significantly decreased heart rate,

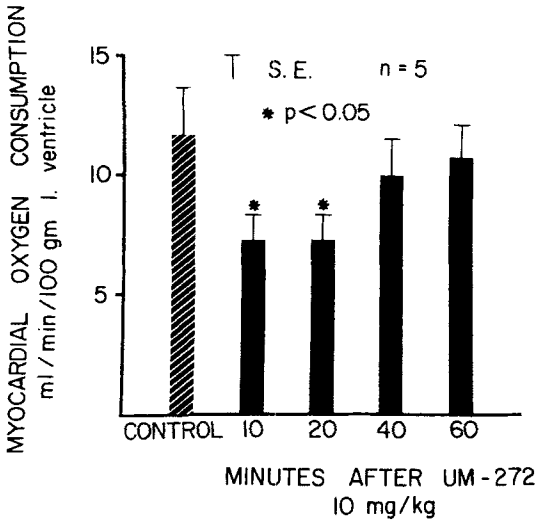

FIG. 22. The effect of pranolium (UM-272) on the myocardial oxygen consumption in anesthetized, open-chest dogs. Myocardial oxygen consumption, calculated and expressed as ml/min/100 g of left ventricle is displayed on the *ordinate*; the time after drug administration is displayed on the *abscissa*. Each bar represents the mean myocardial oxygen consumption ± SE of five separate experiments. Mean control O_2 consumption in these experiments was 11.7 ± 1.9. This was significantly reduced to 7.3 ± 1.1 at 10 min after drug and 7.4 ± 1.0 at 20 min after pranolium. Even though the calculated myocardial oxygen consumptions were not significantly different at 40 and 60 min after drug administration, the values were still below initial control values. (From Kniffen et al., ref. 33, with permission.)

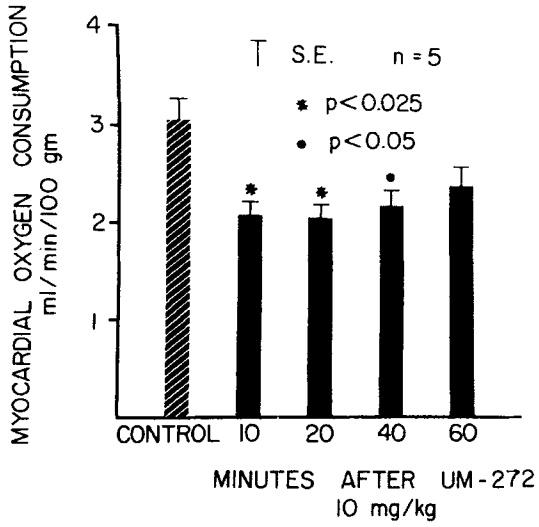

FIG. 23. The effect of pranolium (UM-272) on the myocardial oxygen consumption in isolated, blood-perfused canine hearts. Myocardial oxygen consumption, calculated and expressed as ml/min/100 g of heart, is displayed on the *ordinate*; the time after drug administration is displayed on the *abscissa*. Each bar represents the mean myocardial oxygen consumption ± SE of five separate experiments. Mean control oxygen consumption in this study was 3.1 ± 0.2. This was significantly reduced to 2.1 ± 0.1 at 20 min and 2.2 ± 0.2 at 40 min after drug. Even though the calculated myocardial oxygen consumption was not significantly different at 60 min, the value was still below initial control measurements. (From Kniffen et al., ref. 33, with permission.)

contractile force, myocardial oxygen consumption, and the epi/endo coronary blood flow ratio. Coronary artery perfusion pressure increased significantly. Similar changes were seen 15 min after propranolol (0.5 mg/kg, i.v.) was administered to the donor dog (Fig. 24). In this isolated blood-perfused heart preparation with spontaneous heart rate, the intracoronary administration of pranolium (0.5 mg/min) produced significant stepwise decreases in heart rate and myocardial oxygen demands. At 30, 60, and 120 min after the start of the infusion a stepwise increase in subendocardial blood flow was similarly seen. The above changes were greatest at 30 min after the start of infusion. In contrast, when the heart rate was held constant

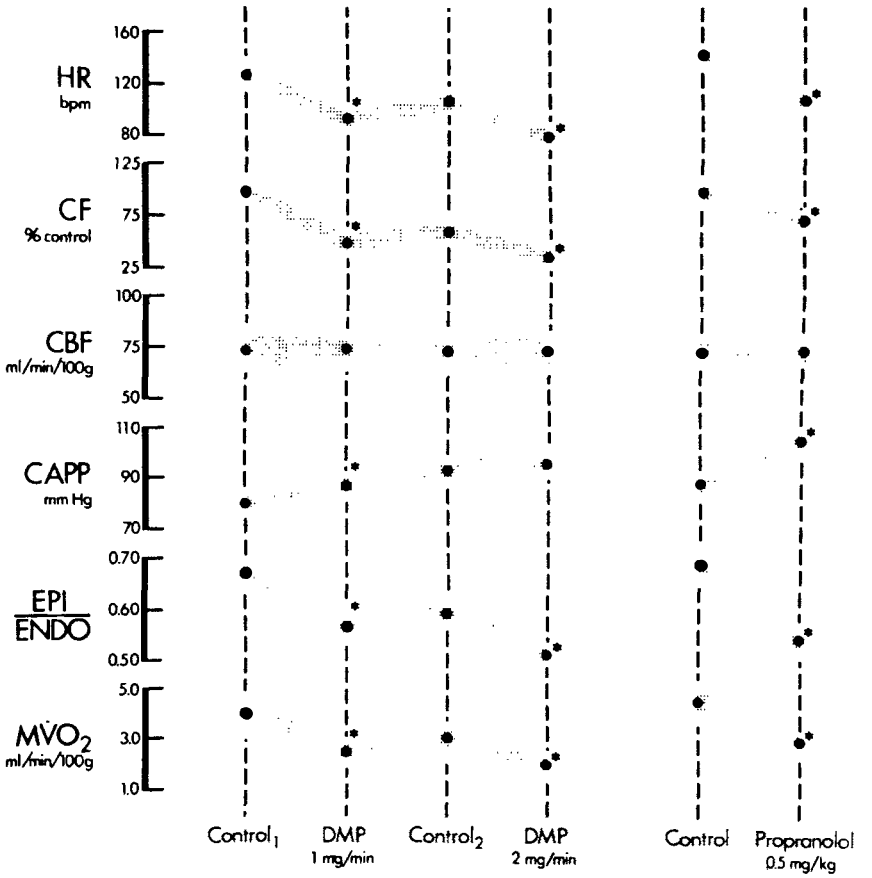

FIG. 24. Effects of pranolium (DMP) on propranolol on myocardial hemodynamics and oxygen consumption. Similar changes in heart rate (HR), contractile force (CF), coronary artery perfusion pressure (CAPP), left ventricular epicardial-endocardial blood flow ratio (EPI/ENDO) and myocardial oxygen consumption (MVO_2) were observed after intracoronary infusions of pranolium for 15 min ($N = 7$) or 15 min after intravenous administration of propranolol ($N = 6$). Coronary blood flow (CBF) was held constant in both groups. Points and shaded areas represent mean ± SEM, respectively. *Significant difference ($p < .05$) from preceding control value by paired comparison. (From Warltier et al., ref. 82, with permission.)

at 150 beats/min by right atrial pacing, the increase in subendocardial perfusion (epi/endo ratio) and the decrease in myocardial oxygen extraction were not as marked as in unpaced hearts.

A significant increase in subendocardial perfusion and a significant decrease in MVO_2 were seen after 30 min of infusion, but the values returned toward control values at 60 and 120 min. The increase in subendocardial perfusion can be attributed primarily to the negative inotropic effect of pranolium, which results in an increased diastolic duration and perfusion time. Propranolol has been shown to produce similar increases in subendocardial perfusion as indicated by a decrease in epi/endo ratio (9,20).

Gross et al. (19) showed that pranolium (1,5, and 10 mg/kg, i.v.) produced a small stepwise increase in the endo/epi ratio of the nonischemic myocardium and a larger increase in the ischemic myocardium. Propranolol had a similar effect in nonischemic and ischemic regions of the left ventricle, but pranolium produced more favorable effects on ischemic subendocardial blood flow.

Both propranolol and pranolium have a negative inotropic effect and limit the severity of epicardial ST-segment elevations after experimental coronary artery occlusion (34). In these experiments, when hearts were paced back to their control levels, propranolol failed to prevent the ST-segment changes. Pranolium, however, reduced the extent of ST-segment changes even when the hearts were paced back to their control state.

Regional Myocardial Ischemia

Several investigators have successfully used pharmacologic interventions to reduce the amount of cardiac tissue susceptible to damage from myocardial ischemia (23,34,40,44,45). Pranolium has been shown to be beneficial in reducing infarct size due to experimental coronary artery occlusion (36,40) in anesthetized open-chest dogs. Lucchesi et al. (40) examined the effect of pranolium in reducing infarct size and electrocardiographic changes resulting from a 60-min occlusion of the left circumflex coronary artery followed by reperfusion. All control animals showed evidence of myocardial ischemia due to coronary artery occlusion as evidenced by ST-segment elevations in a lead II ECG, ventricular premature beats, and ventricular tachycardia. Progressive increases in Q-wave amplitude and loss of R-wave amplitude were seen in all control animals after release of the occlusion (Fig. 25). In pranolium-treated dogs (5 mg/kg, 30 min before occlusion and 2.5 mg/kg every 90 min for a total dose of 15 mg/kg) neither an elevation in the ST-segment nor a loss of R-wave amplitude was observed (Fig. 26). Upon reperfusion, pathologic Q-wave formation was not evident in the treated group. Ectopic beats were significantly reduced in pranolium-treated dogs (15 mg/kg) compared with control animals subjected to LCX occlusion during the first 4 hr of reperfusion. A dose of 12.5 mg/kg similarly reduced ectopic beats, but the effect was not as marked within the hour as with the higher dose. At 24 hr after reperfusion, fewer premature ventricular contractions were seen in pranolium-treated dogs, indicating that many more of the beats were of sinoatrial origin.

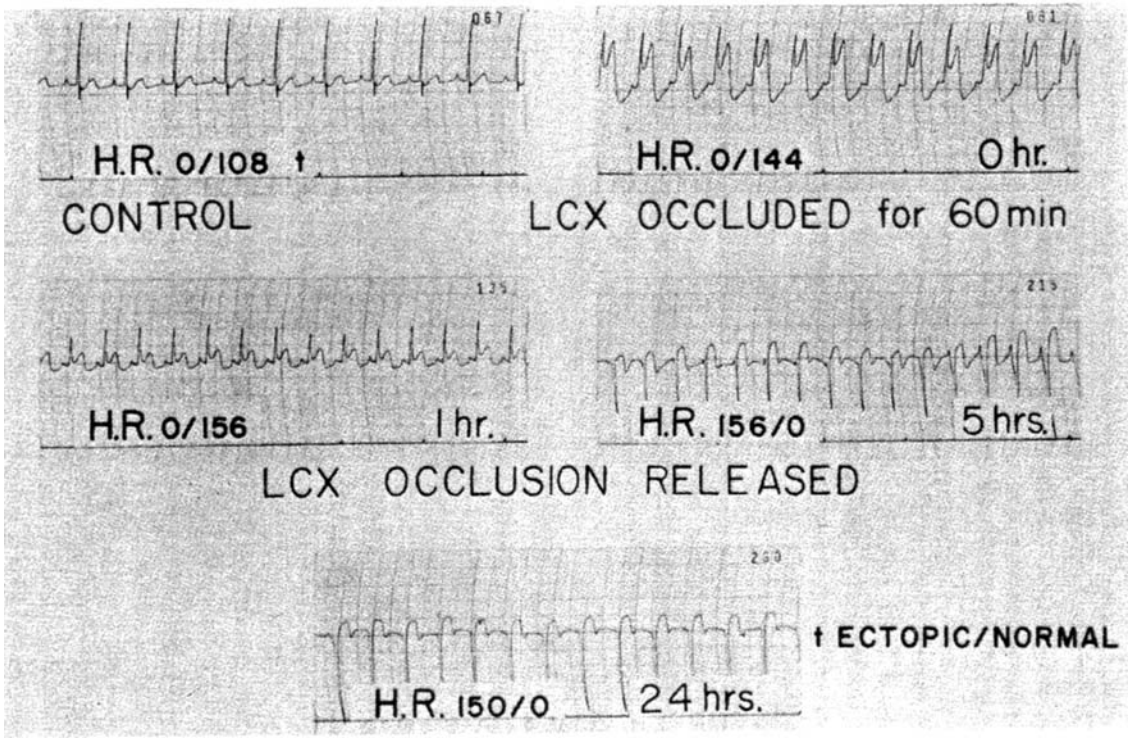

FIG. 25. Experimental myocardial infarction. Sequence of electrocardiographic changes observed after the occlusion of the LCX in the canine heart for 60 min followed by reperfusion of the partially constricted LCX. The *left upper panel* is a lead II ECG tracing taken before coronary artery occlusion. The numerals below indicate the number of ectopic beats over the number of normal beats/min. The ECG shows evidence of ischemic damage as indicated by the elevation in the ST-segment. The two *center panels* were recorded 1 and 5 hr, respectively, after LCX reperfusion. There is progressive loss of R-wave amplitude and an increase in the Q-wave voltage. At 5 hr, the rhythm is entirely abnormal and persists until the next day as shown in the *lower trace* (recorded via telemetry from the conscious animal), 24 hr after reperfusion. (From Lucchesi et al., ref. 40, with permission.)

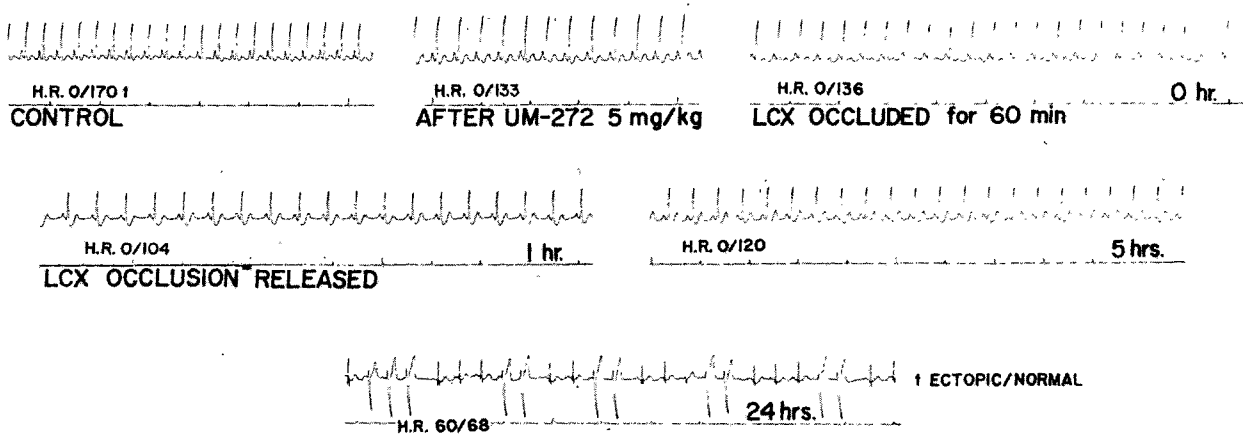

FIG. 26. Experimental myocardial infarction. Sequence of electrocardiographic changes observed in an animal which had been subjected to 60 min of LCX occlusion and reperfusion after pretreatment with pranolium in an initial dose of 5 mg/kg 30 min before occlusion and 2.5 mg/kg every 90 min for a total dose of 5 mg/kg. Each of the panels shows the lead II ECG recording. The numbers in lower left of each panel are the ectopic rate per min over the number of normal beats/min. As noted in the second panel, pranolium produced a slowing of the sinus rate. Occlusion of the LCX and subsequent reperfusion did not give rise to the electrocardiographic changes noted in the control group. During the acute phase, pranolium provides a significant degree of protection against the development of abnormal cardiac rhythms and markedly alters the electrocardiographic changes usually observed in the ST-segment, as well as the morphologic changes in the Q and R waves, suggesting that the heart is protected from extensive ischemic damage. At 24 hr after reperfusion, an abnormality in rhythm is present, but once again it differs from the typical pattern observed in the untreated group in that many of the beats are of sinoatrial origin. (From Lucchesi et al., ref. 40, with permission.)

The technique of tetracycline deposition surrounding the infarcted tissue (25,42,77) was employed to delineate infarcted tissue from noninfarcted tissue. UV examination shows that tetracycline is deposited primarily in the periinfarct tissue forming a fluorescent ring around nonfluorescent or infarcted myocardium. The central portion of the infarct does not show a positive tetracycline stain because of the lack of perfusion to this area. The rim of positive tetracycline stain (fluorescent under UV light) represents that portion of the infarct that has been irreversibly injured due to an ischemic event, but is still being perfused. This area represents viable myocardium that may be salvaged using proper pharmacologic approaches.

NBT (nitroblue tetrazolium), on the other hand, is reduced by dehydrogenase activity in both normal myocardium and the relatively ischemic tissue delineated by tetracycline fluorescence under UV light. These two areas are stained a deep blue, thus allowing delineation of viable and infarcted tissue.

In pranolium-pretreated hearts examination of tetracycline-stained hearts under UV light showed a "patchy" or "nonconfluent" distribution of fluorescent material in the myocardium supplied by the LCX in all but two hearts. The confinement of the fluorescent material to the endocardial region was noted in all but two hearts, and in these hearts the fluorescent material extended to the midmyocardial zone. The NBT stain showed nonstaining areas of myocardium confined to the endocardial zone.

Infarct size determination by gravimetric analysis showed a significant dose-related reduction in the extent of myocardial insult in pranolium-treated animals. The results show that pranolium treatment can significantly reduce the amount of myocardium that undergoes necrosis as a result of a temporary occlusion of the circumflex coronary artery and, in contrast to propranolol, does not produce beta-adrenergic receptor blockade which could compromise cardiac function.

Electrocardiographic changes such as epicardial ST-segment elevations, loss of R-wave amplitude, the development of pathologic Q-waves, and biochemical changes such as the loss of myocardial creatine kinase (CPR) activity have been used to determine and/or predict the extent of myocardial ischemic injury as a result of coronary artery occlusion (14,18,23,31,45,52). Ku and Lucchesi (36) used these parameters along with gravimetric determination of infarct size to assess the effect of pranolium pretreatment in protecting the ischemic heart against irreversible damage.

Dogs were randomized to saline control and pranolium (2 mg/kg given 30 min before LAD occlusion then 2 mg/kg every 90 min for a total intravenous dose of 10 mg/kg) treatment groups. After 90 minutes of LAD occlusion in anesthetized, open-chest dogs, coronary flow was reinstituted gradually so as to reduce the incidence of hemorrhagic infarction and ventricular fibrillation. At 24 hr after reperfusion, dysrhythmias appeared to originate from multifocal ectopic sites in the saline-treated group. In the pranolium-pretreated animals, however, the severity of ventricular dysrhythmias was markedly reduced and abnormal beats appeared to be predominantly unifocal in origin and with a longer R-R interval.

In control and pranolium-treated animals similar increases in ST-segment elevations were observed 15 min after LAD coronary artery occlusion. The development of pathologic Q-waves upon reperfusion, however, was significantly less in pranolium-treated animals versus controls. At 24 hr, pranolium-treated animals had evolved smaller Q-wave voltages compared with the control group. The sum of R-wave voltage decrease and the Q-wave voltage was significantly less in the drug-treated than in the control group.

The loss of myocardial CPK activity, which has been used to quantitate the extent of myocardial infarction (31,45,73,75) was significantly less in pranolium-treated than in the control hearts. This suggests that pranolium treatment resulted in greater salvage of cardiac tissue in response to an ischemic insult. In these studies, infarct size, as measured gravimetrically after NBT staining, was reduced to a greater extent in pranolium-pretreated than in control animals.

The available data show that pranolium protects the ischemic myocardium from irreversible injury. Pranolium was found to reduce myocardial infarct size, decrease voltage in the pathologic Q-wave, reduce the severity and number of premature ventricular contractions, and preserve myocardial CPK and dehydrogenase activities in hearts subjected to regional ischemia and reperfusion.

Global Ischemia—Protective Effects of Pranolium

Vogel et al. (81) have examined the effect of pranolium on myocardial injury during global ischemia in the isolated and blood-perfused cat heart. This model was selected because the isolated preparation allows precise measurement and control of hemodynamic variables, and global ischemia eliminates factors related to collateral coronary artery flow seen during regional ischemia. The use of the globally ischemic heart also simplifies tissue sampling problems associated with experimental models employing regional ischemic injury. Vogel et al. (81) studied several parameters which have been associated with ischemic injury including the presence or absence of contracture, changes in ventricular pressure development and diastolic pressure/volume relationships, fluid and electrolyte accumulation, and microsomal Ca^{2+} accumulation.

Four groups of isolated hearts were studied. A control group ($N = 10$) was not made ischemic and did not receive drug. A group of untreated ischemic hearts ($N = 10$) was subjected to 1 hr of global ischemia followed by 1 hr of reperfusion. Two groups of ischemic hearts received pranolium (0.75 mg/min for 10 min) before ischemic arrest. In one group ($N = 10$), the hearts were allowed to beat spontaneously during drug administration. The second group ($N = 8$) was paced at 150 beats/min.

During an infusion of pranolium to spontaneously beating isolated cat hearts (0.75 mg/min/10 min) there was a decrease in heart rate (135 ± 12 to 85 ± 9 beats/min), coronary blood flow (1.08 ± 0.64 to 0.59 ± 0.48 ml/min/g wet weight), and myocardial oxygen consumption (6.8 ± 1.7 to 2.7 ± 1.7 ml/min/100 g wet weight). In hearts paced at 150 beats/min during pranolium infusion, ventricular

pulse pressure decreased 37% and this was similar to the decrease seen in unpaced hearts (Table 7). However, neither coronary blood flow nor oxygen consumption decreased in the paced hearts (Table 7), suggesting that the decrease in myocardial oxygen consumption seen in spontaneously beating hearts was a result of the negative inotropic effect and not related to the contractile state of the myocardium under conditions in which left ventricular volume was maintained constant with a latex fluid-filled balloon.

Pranolium decreased the severity of myocardial injury in response to global ischemia followed by reperfusion. Contracture during and immediately after global ischemia was decreased by pranolium pretreatment (Table 8) and, in addition, pranolium pretreatment maintained the ventricular diastolic pressure-volume relationship at a level similar to that of the pre-ischemic control (Fig. 27). This suggests that pranolium protects the ventricle from the decrease in compliance normally seen after global ischemia. Pacing the heart at a constant rate during pranolium administration partially reversed the protective effects of the drug on contracture and compliance, suggesting that the fall in heart rate produced by pranolium prior to the onset of ischemia is an important component of pranolium's ability to reduce global ischemic injury (Fig. 27, Table 8). However, pranolium pretreatment was unable to produce any significant recovery in ventricular developed pressure.

Besides its effect on the mechanical properties of ventricular muscle, pranolium reduced the reperfusion-induced hyperemic response at 60 min in nonpaced hearts (Fig. 28), decreased tissue accumulation of Na^+ and Ca^{2+}, and reduced K^+ loss (Table 9). In addition, pranolium preserved both microsomal adenosine triphosphate (ATP)-dependent calcium uptake (Fig. 29) and calcium binding (Table 10). While the mechanism of ischemic contracture is controversial (30), it can be antagonized by manipulations which delay depletion of ATP or which may reduce the availability of calcium to contractile proteins (22). Warren et al. (83) have demonstrated that pranolium can reduce State 3 respiration, so that in the study of Vogel et al. (81), ATP stores may have been preserved by pranolium acting to decrease oxygen consumption independent of its negative chronotropic effect. Pranolium also reduced the augmentation of total myocardial calcium content (Table 9) which occurs upon reperfusion. Although it is not known how calcium was distributed within the myocardium in the pranolium-treated hearts, preservation of the calcium-accumulating ability of the sarcoplasmic reticulum may have maintained normal free calcium concentrations surrounding the contractile apparatus.

While pranolium was not able to preserve all indices of myocardial function (i.e., developed ventricular pressure) the above study demonstrates that the quaternary drug can preserve myocardial viability during global ischemia by reducing myocardial energy requirements before ischemia and possibly through direct actions on myocardial calcium regulation.

TABLE 7. *Effects of ischemia and treatment with pranolium on myocardial oxygen consumption*

	No Rx		Pranolium			Pranolium ± pace		
	Initial[a]	Final[b]	Initial[a]	Post-Rx[c]	Final[b]	Initial[a]	Post-Rx[c]	Final[b]
LVPP[d]	140 ± 26	57 ± 21[d]	138 ± 28	77 ± 23[e]	50 ± 15[e]	142 ± 19	93 ± 19[e]	66 ± 22[e]
CBF	1.0 ± 0.3	1.5 ± 0.3[d]	1.0 ± 0.4	0.4 ± 0.3[d]	0.7 ± 0.5[d]	1.0 ± 0.1	0.9 ± 0.3	1.8 ± 0.7[d]
MVO_2	6.2 ± 3.4	3.3 ± 1.7[d]	6.8 ± 1.7	2.7 ± 1.7[e]	3.5 ± 1.9[e]	5.6 ± 1.1	4.8 ± 1.4	3.6 ± 1.9[d]
(AV) O_2	7.3 ± 2.7	2.2 ± 1.1[e]	8.4 ± 4.4	5.2 ± 2.5	6.6 ± 4.4	5.9 ± 1.9	5.4 ± 1.1	2.2 ± 0.8[e]
EXT	44 ± 3	14 ± 5[e]	52 ± 8	42 ± 11	43 ± 22	41 ± 17	37 ± 11	14 ± 6[e]
D/C	2.4 ± 0.6	8.3 ± 3.9	2.0 ± 0.3	2.4 ± 0.6	2.7 ± 1.2	2.6 ± 0.8	2.8 ± 0.6	8.3 ± 4.7[d]

LVPP, left ventricular pulse pressure, mm Hg; CBF, coronary blood flow, ml/min/g wet weight; MVO_2, myocardial oxygen consumption, ml/min/100 g wet weight; (AV) O_2, arterial-venous oxygen difference, volumes percent; EXT, myocardial oxygen extraction percent; and D/C, ratio of O_2 delivery to consumption $(AO_2 \times CBF)/MVO_2$.

Values are mean ± 95% confidence intervals for five hearts in each group.

[a]Values obtained at the end of the 60 min equilibration period.

[b]Values obtained after 40 min of reperfusion.

[c]Values obtained at the end of the 10 min drug infusion period.

[d]Indicates $p < .05$ compared to initial value by paired *t*-test.

[e]Indicates $p < .005$ compared to initial value by paired *t*-test.

TABLE 8. *Development of contracture during ischemia*[a]

	Ischemia						Reperfusion
	10 min	20 min	30 min	40 min	50 min	60 min	5 min
No Rx	2 ± 2	7 ± 5	12 ± 10	16 ± 9	19 ± 9	25 ± 8	32 ± 10
Pranolium	0 ± 0	1 ± 1	2 ± 2	4 ± 3[b]	8 ± 5[b]	11 ± 9[b]	7 ± 3[b]
Pranolium ± pace	0 ± 0	1 ± 2	2 ± 3	4 ± 4	7 ± 6	12 ± 8[b]	19 ± 11[c]

Values are means ± 95% confidence intervals.

[a]Measured as increase in resting pressure, in millimeters of mercury, with left ventricular balloon volume constant.

[b]Signficantly different from value in untreated hearts.

[c]Significantly different from value in treated hearts which were not paced.

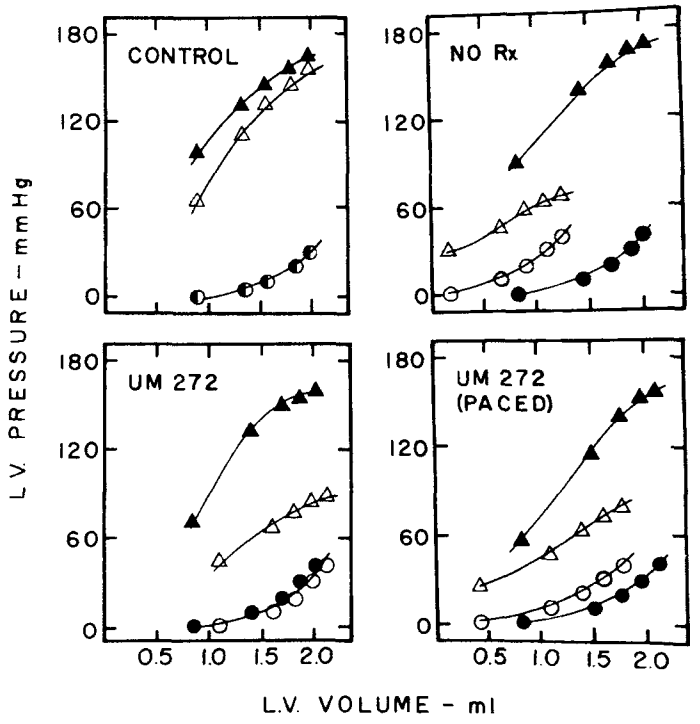

FIG. 27. Summary of diastolic pressure-volume curves and left ventricular (LV) function curves. Diastolic pressure-volume curves are indicated by circles. Ventricular function curves were generated by plotting left ventricular pulse pressure as a function of left ventricular volume as indicated by the *triangles. Solid symbols* represent values obtained in the preischemic period; *open symbols* represent values obtained 1 hr after the end of the ischemic period. Each point represents the mean value of 8–10 hearts. Confidence intervals have been omitted for clarity. (From Vogel et al., ref. 81, with permission.)

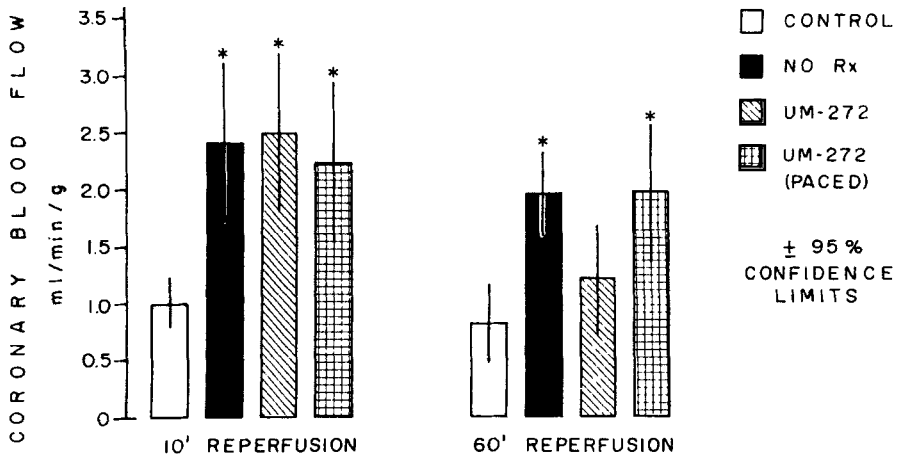

FIG. 28. Coronary blood flow during the reperfusion period, with LVEDP adjusted to zero in all groups. Significant differences between ischemic hearts and nonischemic control hearts are indicated by *($p < .005$). The peak hyperemic response at 10 min of reperfusion was similar in all ischemic groups. At 60 min of reperfusion, coronary flow remained elevated in untreated hearts and in treated-paced hearts but returned toward control values in nonpaced treated hearts. At 60 min, flow in nonpaced, pranolium (UM-272)-treated hearts was significantly less than in either of the other ischemic groups ($p < .001$). Each bar represents the mean of 8–10 hearts. *Vertical lines* indicate 95% confidence intervals. (From Vogel et al., ref. 81, with permission.)

PHARMACOKINETICS

Oral Absorption

Pranolium, in common with other monoquaternary ammonium compounds, is absorbed to a greater extent than could be predicted from its lipid solubility. Pranolium is present in plasma within 10 min after oral administration of 40 or 60 mg/kg to anesthetized dogs (59) (Fig. 30). As with other monoquaternary ammonium compounds (38), there is a nonlinear correlation between the dose administered and the amount absorbed. The extent of absorption of a 60-mg/kg dose of pranolium is about twice that of a 40-mg/kg dose, although both doses were sufficient to convert ouabain-induced ventricular tachycardia to normal sinus rhythm (59) (Fig. 30). One possible explanation for the incomplete absorption of pranolium from the gastrointestinal tract is the presence of a monoquaternary ammonium ion transport system in jejunal mucosa (78). The transport system is capable of transporting monoquaternary ammonium ions from blood to the intestinal lumen and is saturable. The increased bioavailability of pranolium at a dose of 60 mg/kg versus 40 mg/kg may be the result of saturation of this intestinal transport system.

Distribution

Plasma concentrations of ^{14}C-labeled pranolium decrease in a biexponential manner after intravenous administration in anesthetized dogs (16). Pharmacokinetic

TABLE 9. *Myocardial electrolyte content*

	H_2O			Na^+ (μmol/g dry wt)			$(Na^+)_c$ (μmol/g dry wt)			K^+ (μmol/g dry wt)			Ca^{2+} (μmol/g dry wt)		
	$\bar{X}$	95%	*N*	$\bar{X}$	95%	*N*	$\bar{X}$	95%	*N*	$\bar{X}$	95%	*N*	$\bar{X}$	95%	*N*
Intact hearts	76.7	0.4	19	180	14	14	180[a]	14	14	321	12	20	8.5	1.4	17
Isolated hearts															
Control	76.2	0.8	7	188	30	7	188[a]	30	7	309	41	7	8.3	1.8	4
Ischemic															
No Rx	80.2[b]	1.7	7	388[b]	65	9	276[b]	54	9	214[b]	48	9	24.2[b]	5.7	8
Pranolium	79.9[b]	0.8	7	267[b,c]	39	6	181[c]	21	6	309[d]	30	6	12.6[b,c]	4.1	10
Pranolium + pace	80.1[b]	1.0	6	385[b,d]	33	6	276[b,d]	38	6	219[b,d]	44	6	18.4[b,e]	7.7	6

$(Na^+)_c$, sodium content correct for accumulation of edema fluid; $\bar{X}$, mean; 95%, 95% confidence limits; and *N*, number of measurements in each group.

[a]No correction for edema was made in these groups

[b]Signficantly different from value in intact hearts

[c]Significantly different from value in untreated ischemic hearts

[d]Significantly different from treated hearts without pacing

[e]Not significantly different from untreated or treated ischemic hearts

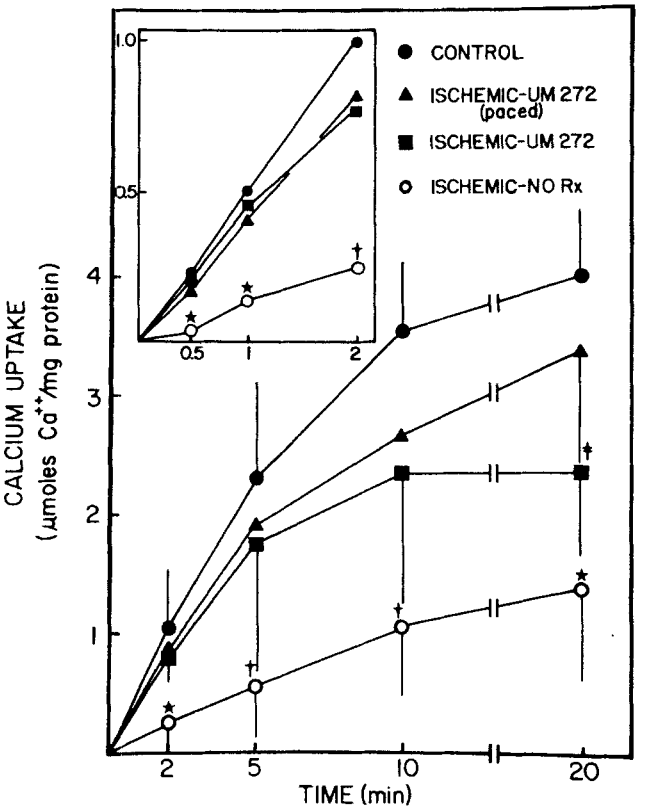

FIG. 29. ATP-dependent $^{45}Ca^{2+}$ uptake by microsomes isolated from cat hearts (N = 8–10) was measured in medium containing 0.1 M KCl; 5.6 mM $MgCl_2$; 5.6 mM potassium oxalate; 100 μM $^{45}CaCl_2$ (0.1 μCi/liter); 5 mM Tris-ATP; and 15 to 40 μg/ml of microsomal protein in 20 mM Tris-maleate buffer, pH 6.8 (37°C). Values shown are means ± 95% confidence limits, based upon duplicate runs, calculated for the four groups of isolated microsomes of cat hearts. Data are corrected for nonspecific binding of $^{45}Ca^{2+}$ to Millipore filters. **Inset**: initial 2 min calcium uptake by cardiac microsomes isolated from the appropriate isolated hearts. With the exception of the ischemic-No Rx group, uptake proceeded linearly with time during this period. *($p < .05$ vs. control, pranolium (UM-272) and pranolium-paced); †($p < .02$ vs. control, pranolium and pranolium-paced); ‡($p < .05$ vs. control). (From Vogel et al., ref. 81, with permission.)

analysis indicates an alpha-phase distribution half-life of 2.1 ± 0.2 min and a beta-phase distribution half-life of 127 ± 10 min. The rapid clearance of pranolium from blood (approximately 11 ml/min/kg) suggests that an active secretory process may be responsible for clearance of pranolium from plasma to urine. Approximately 10% of an intravenously administered dose of ^{14}C-labeled pranolium appears in urine at 2 hr after administration (16). Examination of urine samples by thin-layer chromatography failed to detect metabolites of pranolium. All ^{14}C-labeled activity in urine migrated as a single peak which corresponded to reference ^{14}C-labeled drug.

TABLE 10. *Microsomal calcium binding*

Group	1 min	% Control	5 min	% Control
Control (6)	25 ± 10	100	48 ± 15	100
Ischemia-No Rx (6)	7 ± 6[a]	26	13 ± 12[a]	27
Ischemia-Pranolium (4)	31 ± 17	122	46 ± 23	96
Ischemia-Pranolium (6) (paced)	19 ± 10	74	38 ± 3	79

[a]Indicates significant difference between untreated ischemic hearts and all other groups.

Ca^{2+} binding was assayed under conditions similar to those described in the legend to Fig. 29 except that the $^{45}Ca^{2+}$ concentration was lowered to 20 μM, protein concentration was 40–60 μg/ml, the temperature was 25°C and potassium oxalate was absent from the incubation medium. Values are mean ± 95% confidence limits.

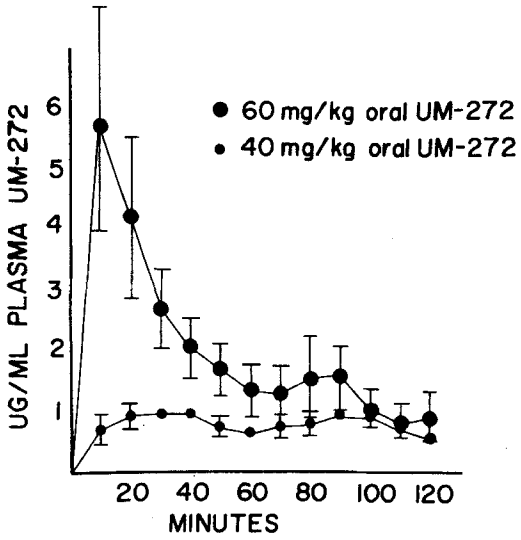

FIG. 30. Plasma pranolium (UM-272) concentrations after p.o. administration. Plasma pranolium concentrations are shown for a period of 2 hr. The area under the curve was more than three times as great in the 60 mg/kg group as the 40 mg/kg group. (From Patterson et al., ref. 59, with permission.)

Pranolium exhibits a large steady-state volume of distribution, 1.6 liters/kg (16), suggesting that extensive binding of the drug occurs in body tissues. Pranolium concentrations in heart, diaphragm, skeletal muscle, and blood were determined 2 hr after intravenous administration of 5 mg/kg ^{14}C-labeled drug, and the data are presented in Fig. 31. Myocardial concentrations of pranolium were 36 times that of blood, 30 times that of skeletal muscle, and 5 times that of the diaphragm (16). Similar selective concentration of drug in heart tissue is observed after oral administration of pranolium. Myocardial concentrations of pranolium after oral administration of 40 or 60 mg/kg ranged from 8 to 35 times that of plasma (59). Table 11 summarizes the data showing myocardial and plasma concentrations observed after intravenous and oral pranolium administration.

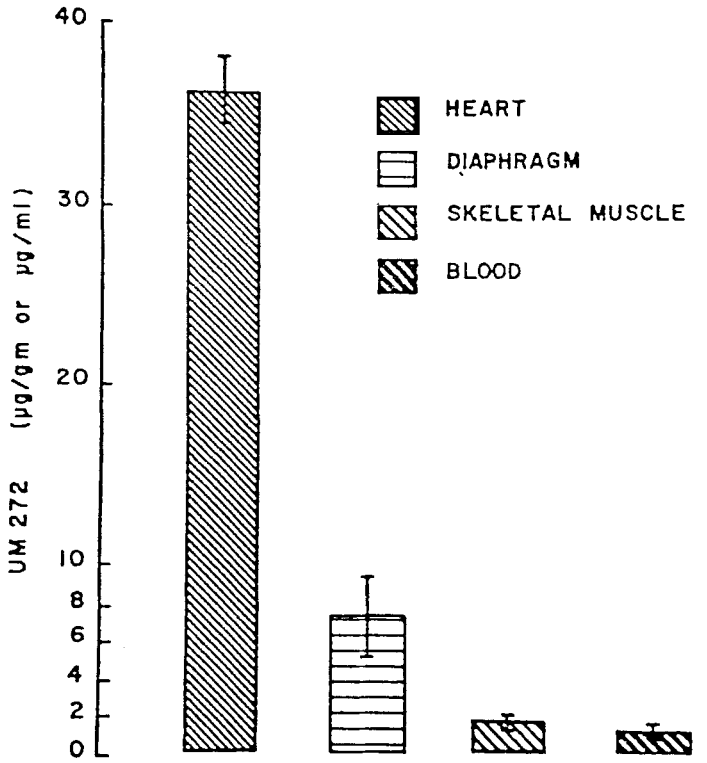

FIG. 31. Pranolium concentrations in various tissues are shown 2 hr after administration. (From Gibson et al., ref. 16, with permission.)

TABLE 11. *Plasma and myocardial pranolium concentrations 2 hr after oral and intravenous administration*

	Plasma (µg/ml)	Myocardium (µg/ml)		Urinary excretion (% dose)
5 mg/kg i.v.	1.0 ± 0.2	Atrial	36.0 ± 3.8	10.0 ± 3.5%
		R. ventricle	34.3 ± 6.7	
		L. ventricle	36.4 ± 1.9	
40 mg/kg p.o.	0.6 ± 0.1	Atrial	18.8 ± 3.0	3.0 ± 0.6%
		R. ventricle	18.8 ± 2.9	
		L. ventricle	18.9 ± 2.9	
60 mg/kg p.o.	0.9 ± 0.5	Atrial	39.0 ± 7.8	9.8 ± 0.9%
		R. ventricle	39.5 ± 6.8	
		L. ventricle	39.3 ± 6.8	

Plasma Concentrations—Therapeutic Response

Although plasma concentrations of pranolium decline rapidly after intravenous administration, a high concentration of pranolium is maintained in myocardium. The plasma concentration at the time of initial conversion of a oubain-induced ventricular tachycardia was 7.2 ± 1.5 μg/ml, but despite its decrease to 1.0 ± 0.2 μg/ml 2 hr later, the arrhythmia did not return. After oral administration, the plasma concentration of 4.2 ± 1.5 μg/ml (60 mg/kg dose) and 0.7 ± 0.2 μg/ml (40 mg/kg dose) were observed at the time of initial conversion of the ouabain-induced ventricular tachycardia to normal sinus rhythm. Lower plasma concentrations of 0.9 ± 0.5 and 0.6 ± 0.1 μg/ml were observed later in the experiment and still exerted significant antiarrhythmic action. Despite the presence of the lower plasma concentrations 2 hr after administration of oral or intravenous pranolium, tissue concentrations remain high (Table 11) and the antiarrhythmic action persists.

Duration of Action

Despite the rapid clearance of pranolium from plasma, the extensive uptake of pranolium in heart tissue extends its duration of action beyond that which could be expected simply based upon plasma concentrations. Significant depression of conduction in normal and ischemically injured myocardium and prolongation of effective refractory periods in normal myocardium are observed 12 hr after a 5- or 10-mg/kg dose. Protection against the induction of reentrant ventricular tachyarrhythmias by programmed electrical stimulation was observed 12 hr after the last pranolium dose (62).

Selective uptake and concentration in myocardium with a prolonged duration of action despite rapid clearance from plasma is seen also with bretylium (3,53), clofilium (39), and methyllidocaine (69,70). All three drugs are quaternary ammonium antifibrillatory agents that are cleared rapidly from plasma by renal mechanisms (4,70), but have extended durations of action of up to 16 hr because of their ability to concentrate in myocardial tissue.

SUMMARY

In a wide variety of animal models, pranolium, the dimethyl quaternary derivative of propranolol, is effective in minimizing or eliminating the deleterious effects of myocardial ischemia. Pranolium reduces ultimate infarct size, decreases the extent of Q-wave and ST-segment changes attendant to ischemia, and reduces the accumulation of Ca^{2+} and contracture after global ischemia. Pranolium is also effective against both automatic and reentrant arrhythmias, and is effective in reducing mortality in a conscious canine model of sudden coronary death. Only one clinical study of pranolium has been performed to date and the results of this study are promising. Clearly, more clinical data as to the effectiveness of pranolium are needed and warranted as this drug may represent an important pharmacologic modality in the prevention of cardiovascular death. Since the major cause of death is

sudden unexpected ventricular fibrillation in patients with recognized or unrecognized ischemic heart disease, there is an urgent need for a prophylactic agent that will exert an antifibrillatory action as opposed to an agent that suppresses premature ventricular ectopic beats—an action which may or may not coincide with an ability to prevent sudden coronary death. Pranolium, a quaternary ammonium compound without beta-adrenergic receptor blocking action, possesses both the antiarrhythmic and antifibrillatory actions which would recommend that its potential be explored further in patients who are at risk of sudden coronary death. Toxicology studies and preliminary clinical trials have provided further reason for being enthusiastic over the possibility that pranolium may serve a useful purpose in reducing the morbidity and mortality associated with ischemic heart disease. Furthermore, its effectiveness in several models of ischemic myocardial injury suggests that pranolium has important potential applications in protecting the ischemic heart from irreversible cellular injury. The drug warrants further exploration at the clinical level in an effort to determine its full potential.

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