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Hemodynamic Effects of Procainamide and Quinidine and the Influence of Beta-Blockade Before and After Experimental Myocardial Infarction[1] (38935)

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Antiarrhythmic agents are often used in combination particularly in drug resistant arrhythmias. Little is known about their hemodynamic interaction. In recent experiments carried out in isolated hearts and intact animals, as well as in humans, the association of beta-blocking and other antiarrhythmic agents was evaluated (1-6). The interest of these combinations is derived from both clinical and pharmacological considerations. In the clinical field, Fors (1) and Stern (2, 3) proposed that propranolol might act synergistically with quinidine, therefore representing a very effective method for the treatment of arrhythmias, especially for the achievement and maintenance of sinus rhythm in patients with atrial fibrillation. In the pharmacological field, Visioli and Bertacinni (4) have recently demonstrated both in the isolated heart and in humans that the negative inotropic effects of these two drugs decrease significantly when they are administered jointly. Recently, these experiments were extended to procainamide and beta-blocking agents (5, 6) and again this combination appeared to reduce the sum of single depressive circulatory effects. So the possibility of summing up the antiarrhythmic effects of these commonly used agents without a parallel summing or synergism of circulatory depression appears fascinating. The goal of this study was to investigate this apparent hemodynamic "antagonism" between two similar antiarrhythmic agents, procainamide and quinidine, and a beta-blocking agent, propranolol, in the intact and in the acute myocardial infarction dog model.

Material and Methods. Techniques Twenty-one mongrel dogs weighing 14-22 kg were premedicated with morphine sulfate, 2 mg/kg, and anesthetized with a mixture of 65 mg/kg chloralose and 400 mg/kg urethane administered intravenously. Additional anesthetic was given when corneal reflexes were noted, and control hemodynamic values were reestablished before subsequent study. The animals were intubated with a cuffed endotracheal tube and respiration was maintained with a Harvard respirometer using room air. Body temperature was maintained in a normal range with a fluid-filled blanket. The chest was opened through a midsternal thoracotomy and the pericardium was incised to expose the heart. The right external jugular vein was cannulated with a PE260 catheter[2] and used for drug and fluid administration. The dog was instrumented for measurements of left atrial, aortic and left ventricular pressure, left ventricular dp/dt and aortic flow as previously described (7). Lead II of the electrocardiogram was monitored and heart rate determined during each phase of the study. Arterial blood samples were obtained before each drug intervention for determination of pO_2, pCO_2, and pH using a model AME-1 Astrup blood analyzer.[3] All hemodynamic measurements and recordings were obtained with a Honeywell multichannel model 1508 Visicorder. Systemic resistance was calculated dividing the mean aortic pressure by the cardiac output. All animals were

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[2] Radiopaque polyethylene tubing, Becton Dickinson.

[3] Radiometer Copenhagen, Siggard-Andersen.

housed, fed, anesthetized, and instrumented identically.

Drug study protocol. All animals received 8 ml/kg 6% Dextran 70 after instrumentation was completed and control measurements were taken 20 min later. Dogs were then assigned to two study groups: Group I (eight intact dogs) comprises two subgroups of four dogs who received either procainamide (IA) or quinidine (IB). The myocardial infarction was produced in 13 other dogs (group II) by a technique previously described (8). It consists of a ligation of the largest branch of the left circumflex artery as close as possible to its origin. Following this, serial ligation of diagonal branches of the left anterior descending artery not specifically supplying the septum was accomplished over a 20-min period. Despite this precaution, five dogs died of ventricular fibrillation. The remaining eight dogs survived, and after a 40-min period to allow hemodynamic stabilization, they were equally divided in two subgroups of four animals who received either procainamide (IIA) or quinidine (IIB) as in group I.

Procainamide (30 mg/kg) or gluconate of quinidine (10 mg/kg) was administered intravenously by means of a Harvard pump over a 5-min period. Hemodynamic parameters were monitored at 5-min intervals following the end of the drug infusion. Maximal drug effects occurred immediately at the end of the infusion in most animals and near-control values were always reestablished 30 min later. Then, *d-l* propranolol 1 mg/kg was given intravenously as a bolus. Adequate degree of blockade was determined in each animal by the administration of .4 mg/kg isoproterenol given as an intravenous bolus before and after propranolol. The degree of blockade achieved was at least 90%, since isoproterenol failed to increase the heart rate by more than 10% (9). The same quantity of procainamide or quinidine was then reinfused 30 min after the administration of propranolol in animals of both subgroups A and B approximately 1 hr after the first infusion.

Extent of infarction. At the end of each study, the extent of infarcted myocardium was determined in the eight animals of group II by injecting Evans blue solution into the right and left coronary arteries through the ostia, at a mean pressure of 100 mmHg. The left ventricular free wall and septum were then dissected free from the remainder of the heart. The unstained, unperfused, and infarcted portion of the left ventricle and septum was separated from the stained, uninfarcted muscle, weighed and expressed as percent weight of the total left ventricular free wall and interventricular septum (10).

Statistical analysis. The data were analyzed with an IBM 360/50 digital computer programmed to calculate means and standard errors, using paired and unpaired t tests for determination of significance. In determining the effects of procainamide and quinidine in animals with prior β-blockade, comparisons were made to baseline values obtained after β-blockade had been induced.

Results. I—Hemodynamic effects of procainamide and quinidine before and after β-blockade in the intact animal (group I). Results of these hemodynamic effects are given in Table I, in Fig. 1 for the procainamide subgroup and Fig. 2 for the quinidine subgroup. Prior to β-blockade, both procainamide and quinidine reduced mean arterial pressure significantly ($P < 0.05$) and to a similar degree: -29% and -31% after procainamide and quinidine, respectively. For a comparable decrease in blood pressure, quinidine had markedly different hemodynamic effects; it produced a substantial reduction of 47% in systemic vascular resistance ($P < 0.05$) while heart rate, cardiac output, and dp/dt all increased significantly ($P < 0.05$): $+14\%$, $+35\%$, and $+29\%$, respectively. In contrast, procainamide did not affect systemic vascular resistance. However, heart rate, cardiac output, and dp/dt all significantly decreased ($P < 0.05$): -12%, -29%, and -40%, respectively. Left atrial pressure decreased significantly after quinidine (-13%, $P < 0.01$), but increased after procainamide ($+22\%$, $P < 0.05$).

The administration of propranolol pro-

TABLE I. EFFECTS OF PROCAINAMIDE AND QUINIDINE BEFORE AND AFTER PROPRANOLOL IN INTACT ANIMALS (GROUP I)[a].

Procainamide (IA) Four dogs

Measurement	Control	Proc. 1	New control	Propr.	Proc. 2	Proc. 1 vs Proc. 2
LV dp/dt mmHg/sec	6425 ±1320	3813* ±768	6000 ±1397	2100* ±387	1200* ±191	NS
CO L/min	4.5 ±.3	3.3* ±.3	4.8 ±.3	2.7* ±.4	1.8* ±.4	NS
HR beats/min	190 ±11	198** ±11	198 ±11	193** ±14	153* ±15	NS
LAP mmHg	9.5 ±.9	11.5* ±.8	9.8 ±.8	15.3** ±1.7	18.3** ±1.7	NS
MAP mmHg	119 ±2	84** ±5	116 ±4	117 ±6	80** ±10	NS
SVR units	27 ±3	27 ±2	27 ±2	46* ±6	48 ±6	NS

Quinidine (IB) Four dogs

	Control	Quin. 1	New control	Propr.	Quin. 2	Quin. 1 vs Quin. 2
LV dp/dt mmHg/sec	4075 ±415	5225* ±419	4250 ±393	1575** ±149	988** ±120	$P < 0.01$
CO L/min	2.4 ±.3	3.3** ±.3	3.1 ±.1	2.4* ±.2	2.5 ±.4	$P < 0.05$
HR beats/min	168 ±6	190** ±7	170 ±7	105** ±7	90** ±7	$P < 0.01$
LAP mmHg	9.8 ±.9	8.5** ±.8	8 ±1.2	11* ±1.8	13.5* ±2.3	$P < 0.01$
MAP mmHg	115 ±4	80** ±4	101 ±5	93 ±7	70* ±7	NS
SVR units	49 ±2	25* ±2	33 ±3	39* ±3	29** ±2	$P < 0.05$

[a] Abbreviations: LV dp/dt: rate of rise of left ventricular pressure; CO: cardiac output; HR: heart rate; LAP: left atrial pressure; MAP: mean aortic pressure; SVR: systemic vascular resistance. All values are means ± standard error of the mean. Paired t test: * = $P < 0.05$; ** = $P < 0.01$; NS = no significance. Data obtained after propranolol (propr.) are compared to new control values and data obtained after the reinfusion of procainamide (proc. 2) or quinidine (quin. 2) are compared to the postpropranolol values. A comparison is also made between the effects of procainamide or quinidine before (no. 1) and after (no. 2) propranolol.

duced marked depressive circulatory effects in all animals, and of similar magnitude in the two subgroups A (Fig. 1) and B (Fig. 2) of animals of group I (see also Table I).

The administration of procainamide or quinidine was repeated after β-blockade in the same animals. Both procainamide (Fig. 1) and quinidine (Fig. 2) had similar depressive circulatory effects. After procainamide, dp/dt, heart rate, and mean aortic pressure were decreased by 41%, 15%, and 33%, respectively, and left atrial pressure increased by 22%. Following quinidine, there was a decrease of 38%, 14%, and 24%, respectively, for dp/dt, heart rate, and mean aortic pressure, and left atrial pressure increased by 23%. All the above changes were significant changes from the postpropranolol control values (Table I). In contrast, systemic vascular resistance was not affected by procain-

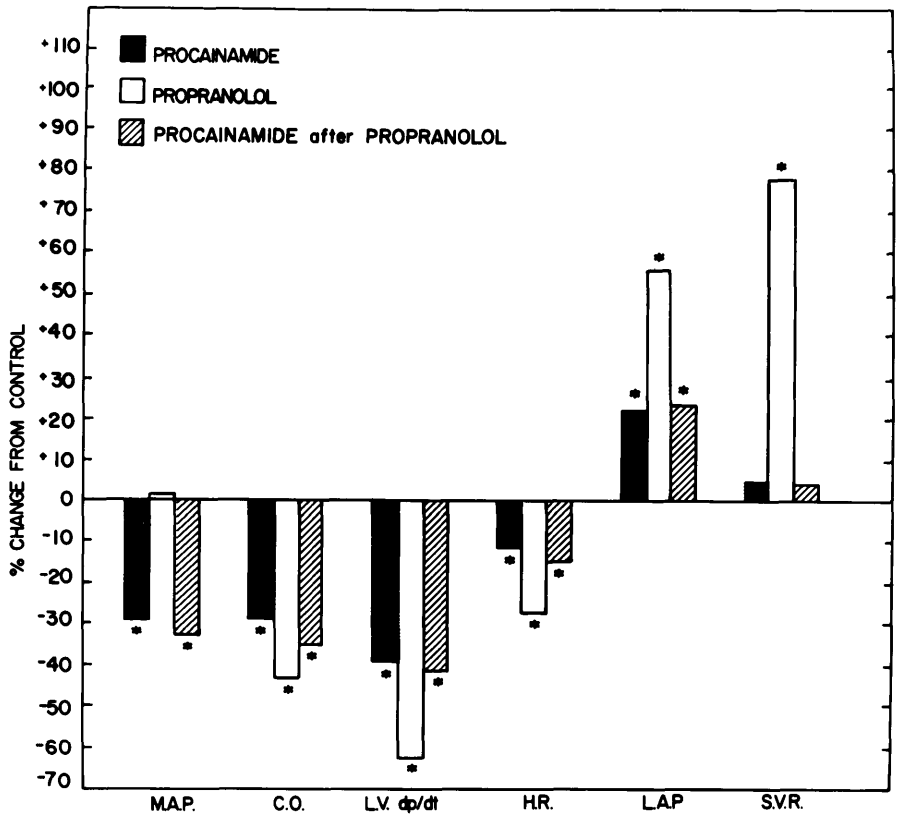

FIG. 1. Hemodynamic changes after administration of procainamide and propranolol before coronary artery ligation, expressed in percentage changes. All values are means for four animals. Note the greater depressive effect of propranolol than that of procainamide but the depressive effect of the latter is not affected by prior administration of propranolol. Statistically significant ($P < 0.05$) changes from control are indicated by an asterisk. The solid triangle indicates a statistically significant change between pre and postpropranolol effects of procainamide. Abbreviations as in Table I.

amide, while it decreased markedly after quinidine (−25%, $P < 0.05$). Cardiac output decreased only after procainamide (−34%, $P < 0.05$) and remained the same after quinidine (+3%).

These depressive effects of procainamide still persisting after β-blockade were not significantly different from the pre-β-blockade changes (Fig. 1). However, when reinfused after propranolol, quinidine produced opposite circulatory effects upon the dp/dt and heart rate which decreased while left atrial pressure increased. These very different effects were statistically different from the prepropranolol effects of quinidine (Fig. 2). On the other hand, although systemic vascular resistance was less diminished after quinidine following propranolol (−25% *vs* −47%), cardiac output was still well maintained. These opposite effects of quinidine after β-blockade occurred despite a similar reduction in mean aortic pressure.

II—Hemodynamic effects of coronary artery ligation. Ligation of coronary arteries produced a uniform, long-lasting response in all eight surviving dogs of group II (Table II). The decreases in cardiac output and dp/dt were nearly identical for the two subgroups A and B, the respective mean changes being −37% cardiac output and −21% dp/dt for the procainamide subgroup (IIA), and −40% and −22% for the quinidine subgroup (IIB). However, coronary artery ligation produced a greater diminution in mean aortic pressure (−16%)

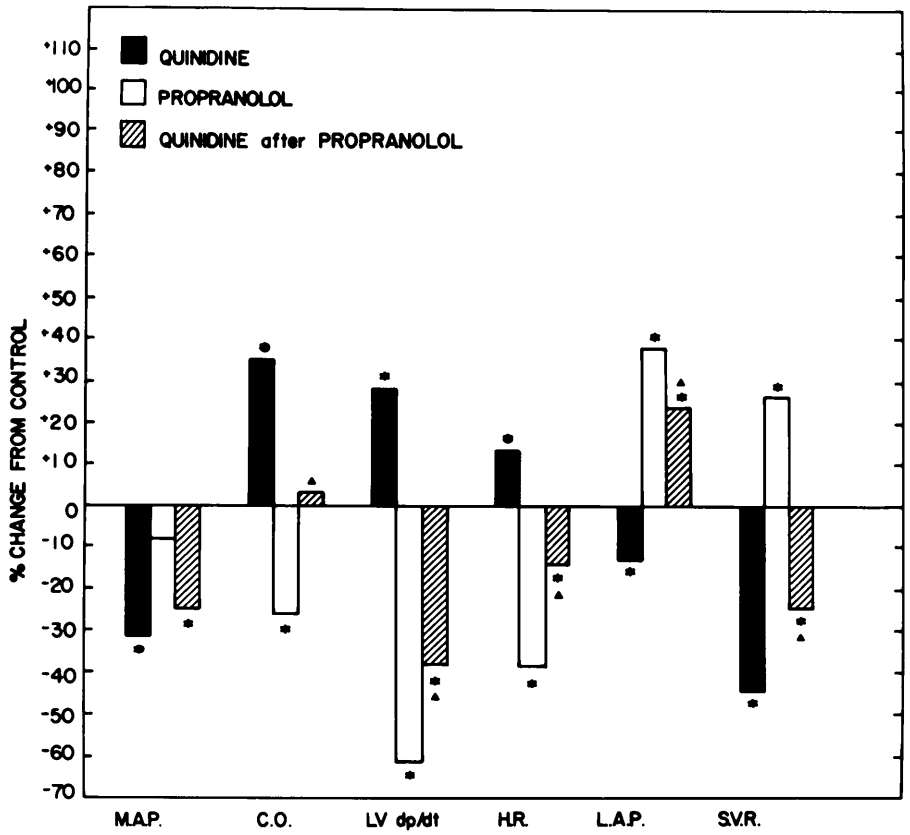

FIG. 2. Hemodynamic changes after administration of quinidine and propranolol before coronary artery ligation. For explanations, see Fig. 1. Note the greater depressive effects of propranolol. After propranolol, for a similar decrease in blood pressure, quinidine clearly produces adverse circulatory effects although systemic vascular resistances are decreased and cardiac output well maintained.

TABLE II. RESPONSE TO CORONARY ARTERY LIGATION IN EIGHT ANIMALS (GROUP II) BEFORE THE ADMINISTRATION OF PROCAINAMIDE-PROPRANOLOL (SUBGROUP IIA) OR QUINIDINE-PROPRANOLOL (SUBGROUP IIB).[a]

	Subgroup IIA			Four dogs	Subgroup IIB			Four dogs
Measurement	Preinfarction control	Response	% Change	Significance of % change	Preinfarction change	Response	% Change	Significance of % change
LV dp/dt mmHg/sec	4425 ±848	3500 ±662	−20.6 ±1.9	$P < 0.05$	3675 ±236	2850 ±185	−22.4 ±1.3	$P < 0.01$
CO L/min	3.4 ±.8	2.1 ±.4	−36.6 ±3.5	$P < 0.05$	3.5 ±.4	2.1 ±.2	−40.0 ±7.5	$P < 0.01$
HR beats/min	190.0 ±10.8	197.5 ±11.1	+4.0 ±1.4	NS	143.0 ±6.0	178.0 ±10.1	+26.0 ±8.0	$P < 0.05$
LAP mmHg	6.25 ±1.1	8.5 ±1.2	+38.7 ±5.9	$P < 0.01$	8.3 ±.3	10.3 ±1.0	+23.6 ±7.5	$P < 0.05$
MAP mmHg	118.0 ±4.1	109.0 ±9.5	−7.8 ±1.7	$P < 0.05$	124.0 ±15.1	106.0 ±17.4	−16.0 ±4.8	$P < 0.05$
SVR units	38.5 ±2.3	46.2 ±5.0	+28.3 ±2.2	$P < 0.05$	38.5 ±9.6	51.5 ±8.9	+40.0 ±10.0	$P < 0.05$

[a] Abbreviations as in Table I.

TABLE III. EFFECTS OF PROCAINAMIDE AND QUINIDINE BEFORE AND AFTER PROPRANOLOL IN LIGATED ANIMALS (GROUP II).[a]

Procainamide (IIA) Four dogs

Measurement	Control	Proc. 1	New control	Propr.	Proc. 2	Proc. 1 vs Proc. 2
LV dp/dt mmHg/sec	4025 ±638	3150* ±603	4125 ±719	1750* ±189	1175** ±131	NS
CO L/min	2.7 ±.5	2.2* ±.5	3.2 ±.5	1.8* ±.5	1.4** ±.4	NS
HR beats/min	193 ±14	153* ±15	193 ±5	128** ±3	108* ±3	NS
LAP mmHg	11 ±.9	13** ±.9	12.3 ±1.2	17* ±1.3	2.2* ±1.3	NS
MAP mmHg	118 ±4	96* ±2	112 ±4	112 ±4	90* ±4	NS
SVR units	48 ±8	54 ±16	37 ±5	73* ±14	82 ±20	NS

Quinidine (IIB) Four dogs

	Control	Quin. 1	New control	Propr.	Quin. 2	Quin. 1 vs Quin. 2
LV dp/dt mmHg/sec	2850 ±185	6100* ±1200	4000 ±642	1550* ±166	1050** ±126	$P < 0.01$
CO L/min	2.6 ±.4	3.5* ±.5	3.1 ±.4	2.1** ±.3	2.7* ±.4	NS
HR beats/min	150 ±13	202* ±6	168 ±6	98** ±6	95 ±5	$P < 0.05$
LAP mmHg	10.4 ±1	7.5* ±.8	7.5 ±.9	13.3* ±2.5	18.8* ±2.5	$P < 0.01$
MAP mmHg	122 ±8	100* ±14	111 ±6	92 ±14	68** ±12	NS
SVR units	48 ±11	29* ±4	37 ±7	46* ±9	26** ±6	NS

[a] Abbreviations and explanations as in Table I.

and a greater increase in heart rate (+26%) and systemic vascular resistance (+40%) in the quinidine subgroup than in the procainamide subgroup (−8% mean aortic pressure, +4% heart rate and +28% systemic vascular resistance). All these changes were significantly different from control values ($P < 0.05$); except the change in heart rate in the procainamide subgroup. The extent of myocardial infarction by weight in the quinidine group was higher (39% ± 3) than in the procainamide group (33% ± 3).

III—Hemodynamic effects of procainamide and quinidine before and after β-blockade in coronary ligation animals (group II). In eight animals who survived an acute myocardial infarction, the same drug protocol was used to determine whether or not the effects of these agents were similar in the acutely depressed animals. These data are shown in Table III, in Fig. 3 for the subgroup A (procainamide) and Fig. 4 for the subgroup B (quinidine).

Procainamide, in the presence of β-blockade, produced a decrease in dp/dt (−33%), cardiac output (−27%), heart rate (−16%), and mean aortic pressure (−20%), while left atrial pressure increased by 28%. These changes were significant changes ($P < 0.05$) when compared to the postpropranolol control values but not when compared to the effects of procainamide prior to β-blockade. Systemic vascular resistance was un-

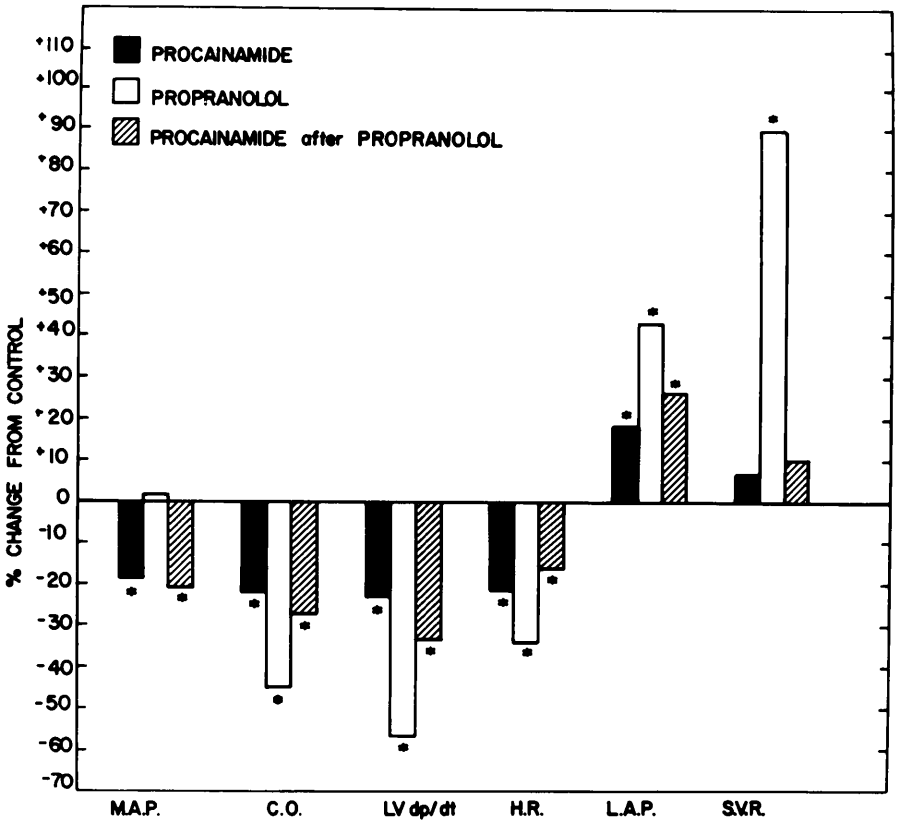

FIG. 3. Hemodynamic changes after administration of procainamide and propranolol after coronary artery ligation. Explanations and comments same as in Fig. 1.

changed by procainamide before and after β-blockade.

Quinidine, in the presence of β-blockade, produced a decrease in dp/dt (−33%, $P < 0.01$), a rise in left atrial pressure (+48%, $P < 0.05$) while heart rate did not change. This is in contrast with the effects of quinidine administered before β-blockade where dp/dt increased by 110% ($P < 0.05$), heart rate by 38% ($P < 0.05$), while left atrial pressure decreased by 27% ($P < 0.05$).

The administration of propranolol did not prevent the effects of quinidine on mean aortic pressure and systemic vascular resistance. Mean aortic pressure decreased by 18% ($P < 0.05$) after quinidine alone and it also decreased after quinidine with propranolol (−27%, $P < 0.01$). Similarly, systemic vascular resistance fell by 37% ($P < 0.05$) after quinidine alone, and by 45% ($P < 0.01$) after quinidine with propranolol. The quinidine increase in cardiac output seen before β-blockade was also observed after β-blockade.

IV—Antiarrhythmic effects. Ventricular premature beats occurred frequently in the eight animals surviving the myocardial infarction. Both procainamide and quinidine were very effective in reducing the ventricular premature beats and no apparent difference was noted between the two. Five other animals developed ventricular fibrillation during coronary artery ligation and were not included in the study.

Discussion. The use of left ventricular dp/dt to estimate the state of cardiac contractility when heart rate, filling pressure, and peripheral vascular resistances are permitted to change is fraught with error (11). Our intent, however, was to study the overall circulatory effects of these agents in conditions under which they are frequently used in man, more specifically in the clinical setting of acute infarction. Directional

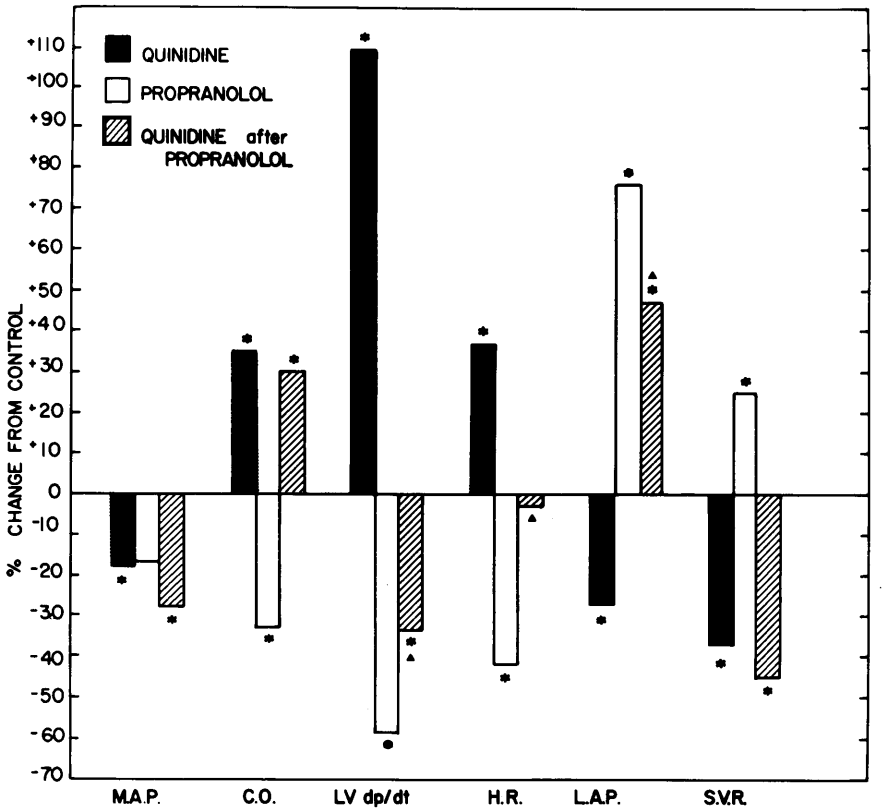

FIG. 4. Hemodynamic changes after administration of quinidine and propranolol after coronary artery ligation. For explanations, see Fig. 1. Comments are similar to those in Fig. 2.

changes are then the only factors considered significant, and these quantitative measures of left ventricular inotropic state are not attempted.

Although the purpose of this study was not to compare the negative inotropic effects of these antiarrhythmic compounds, we attempted to give equal antiarrhythmic and equicardiodepressor doses of procainamide and quinidine for comparison of their interaction with β-blockade, the effective dosage of procainamide being two to three times that of quinidine (12). It should be noted that effective antiarrhythmic doses of these various agents in dogs with acute myocardial infarction are higher than for man (13); the doses used were therefore larger. Several authors also have recommended administration of large amounts of either procainamide or quinidine to achieve successful control of severe arrhythmias in man (14).

This study demonstrated the individual depressive circulatory effects of quinidine, procainamide, and propranolol in the dog, either before or after experimental myocardial infarction by coronary artery ligation, and are in accordance with other studies (7, 15–19). Before β-blockade, procainamide and quinidine showed different effects on the observed parameters, except mean arterial pressure which was similarly decreased. Procainamide given prior to β-blockade had adverse hemodynamic effects, as manifested by significant decreases in dp/dt, cardiac output, heart rate, and significant increases in left atrial pressure. In contrast, quinidine administered before propranolol resulted in marked increase in left ventricular dp/dt and cardiac output in all animals. The etiology of these changes is unclear; the increase in cardiac output and left ventricular dp/dt could be due to acceleration of the heart rate, reflexly medi-

ated through a decrease in aortic pressure (afterload), or directly through the vagal blocking action of quinidine (20). Mechanisms of quinidine causing decreased systemic vascular resistance are complex and apparently involve both a direct dilating effect on vascular smooth muscle and an α-adrenergic receptor blocking effect (21, 22). Although quinidine is classically considered an agent which depresses the contractility of the heart (20), a positive inotropic effect of quinidine has also been reported in dog hearts *in situ* (23), and isolated rabbit atria (24).

The use of propranolol with procainamide did not prevent the adverse circulatory effects of each single compound, either before or after acute coronary ligation. This is in discordance with other preliminary studies (5, 6). Although procainamide has been occasionally shown to have a positive inotropic effect (25), it is generally considered to be a negative inotropic agent. The persistent depressive effect of procainamide in the presence of β-blockade is explained by the different sites of action of the two drugs: propranolol depresses myocardial contractility mainly by its indirect action on the sympathetic innervation of the heart while procainamide has a direct depressive effect on myocardial contractility (25).

The hemodynamic effects of quinidine after β-blockade were different from the effects of quinidine before β-blockade, despite a similar decrease in blood pressure. Quinidine after propranolol caused no increase in heart rate; this lack of heart rate increase probably explains the decrease in dp/dt. However, it was interesting to note that the beneficial effects of quinidine on systemic vascular resistances and cardiac output were not altered by the β-blockade, especially in the coronary artery ligated group. This is in contrast with the effects of the interaction of procainamide-propranolol, although the pharmacodynamic activity of quinidine is similar to procainamide, i.e., anesthetic-like properties and sympatholytic activity. As mentioned earlier, explanations for this quinidine effect on cardiac output and systemic vascular resistances are largely obscure; the role of myocardial α-receptors (26), which is still to be established, must be considered, and also the prominent sympatholytic α-blocking effect of quinidine (27). Therefore, agents able to decrease systemic vascular resistance, such as quinidine, could have beneficial effects on cardiac output (28).

The second dose of each drug was given at a time interval of approximately 1 hr after the first dose, as is often the case with the use of antiarrhythmic agents. There may be an additive hemodynamic effect of the two doses of procainamide or quinidine. The effects of the second dose did not seem to be attenuated by the prior administration of propranolol.

It is not uncommon to administer quinidine or procainamide with propranolol to patients with acute myocardial infarction and severe arrhythmias. Experimental myocardial infarction by coronary artery ligation in the dog can only approximate conditions in man. However, this study suggests that the administration of propranolol does not reduce the circulatory depression produced by procainamide. The combined use of quinidine and propranolol also has a negative circulatory effect, not as marked as the effects observed after procainamide with propranolol.

Summary. The use of antiarrhythmic drugs in combination has been limited because of possible side effects secondary to myocardial depression in the acute myocardial infarction patient. Therefore, we investigated in intact dogs (group I) the hemodynamic interaction of propranolol plus procainamide (subgroup A) or quinidine (subgroup B) and in dogs after experimental myocardial infarction produced by coronary artery ligation (group II).

Infusion of procainamide (30 mg/kg over 5 min) in animals of group IA produced a significant ($P < 0.05$) decrease of 30% in mean aortic pressure, a decrease of 40% in left ventricular dp/dt and 29% in cardiac output. When procainamide was reinfused after propranolol (1 mg/kg), its hemodynamic effects were not significantly different from those observed before propranolol in both groups IA and IIA.

Infusion of quinidine (10 mg/kg over 5 min) in animals of group IB (intact dogs) also produced significant decreases of 24% in mean aortic pressure and 38% in dp/dt while cardiac output was unchanged. However, these hemodynamic changes were seen only after beta-blockade and were significantly different from those obtained before propranolol, where heart rate increased by 14%, dp/dt by 30%, and cardiac output by 35%. These changes occurred despite a similar reduction in mean aortic pressure. This drug combination produced similar response in animals after coronary artery ligation (group IIB).

In conclusion, we feel that the administration of propranolol does not prevent the depressive circulatory effects of procainamide. The combined use of quinidine and propranolol also has a negative circulatory effect although not as marked as the effects observed after procainamide with propranolol.

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