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DUAL ADRENERGIC BLOCKADE AND EPINEPHRINE INFUSION

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ABSTRACT

NASH, CLINTON B.: Dual adrenergic blockade and epinephrine infusion. J. Pharmacol. Exp. Therap. **162**: 246–253, 1968. The effects of *alpha, beta* and dual adrenergic blockade on toxic amounts of epinephrine were studied in anesthetized dogs receiving a 2-hr. i.v. infusion of epinephrine (10 μg/kg/min). Dual blockade by phenoxybenzamine (7.5 mg/kg) and propranolol (2 mg/kg) nearly eliminated blood pressure alterations by epinephrine. As the dose of phenoxybenzamine was reduced in combination with propranolol (2 mg/kg), the pressor response to epinephrine progressively increased. The myocardial hemorrhage produced by epinephrine alone was increased by propranolol, unchanged or slightly reduced by phenoxybenzamine and eliminated by dual adrenergic blockade. The epinephrine-induced effects of pericardial effusion, cardiac arrhythmias, electrocardiogram voltage depression, acidemia and death could all be prevented by adequate dual adrenergic blockade without complete loss of pressor response.

The damaging effects of epinephrine infusions in animals include myocardial hemorrhage, acidosis, cardiac arrhythmias, shock and cardiovascular collapse (Nash and Carter, 1967). Well documented evidence indicates that infusions of norepinephrine produce similar effects (Szakacs and Cannon, 1958; Guernsey and Connolly, 1963). That such toxic effects may also apply to man under clinical conditions has been emphasized repeatedly by Szakacs *et al.* (1959) and Raab (1953).

The production of hemorrhagic myocarditis by catecholamines has intrigued a number of workers, but only an occasional report offered any means of avoiding such damage. Nash and Carter (1967) have shown that reserpine, atropine or bilateral vagotomy did not alter the myocardial hemorrhage produced by infusions of either epinephrine or norepinephrine. Mazzella *et al.* (1964) claimed that phenoxybenzamine would eliminate cardiac hemorrhage produced in dogs by repeated carotid occlusion, and Waters and de Suto-Nagy (1950a) and Maling *et al.* (1964) reported that *alpha* adrenergic blockade prevented cardiac hemorrhage and necrosis induced in dogs by catecholamines.

The recent advent of potent and rather specific *beta* adrenergic blocking agents has opened many new areas of study. Our knowledge of the potential effects of *beta* blockade is still hazy, and information regarding the effects of combined *alpha* and *beta* blockade is scanty, indeed. Consequently, this study was undertaken to investigate the effects of dual adrenergic blockade on epinephrine infusions, with special attention to the hemorrhagic effect on the heart.

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METHODS. Mongrel dogs of either sex were anesthetized with pentobarbital sodium (30 mg/kg i.v.). Arterial blood pressure was measured from the carotid artery *via* a Statham transducer. Respiratory rate was recorded by a Grass PT-5 transducer connected to the side arm of a tracheal cannula, and the lead II electrocardiogram was obtained from needle electrodes. All parameters were recorded with a Grass polygraph recorder. Blood samples were withdrawn from the femoral vein at intervals for measurement of pH and hematocrits.

Epinephrine bitartrate, plus a small amount of glycine as an antioxidant, was dissolved in 0.9% sodium chloride solution in a concentration such that, when infused i.v. (Harvard syringe pump) at a rate of 0.123 ml/min, the animals received 10 μg/kg/min of the alkaloid. Phenoxybenzamine HCl was dissolved in a mixture of 1 ml of 95% ethyl alcohol and 1 ml of propylene glycol, diluted to 5 ml with water and injected i.v. 45 min prior to the beginning of the epinephrine infusion. When propranolol HCl was used, it was dissolved in 0.9% sodium chloride solution and injected i.v. 10 min prior to the epinephrine infusion.

The 40 experimental animals were grouped as

follows: group 1, controls receiving only epinephrine infusion; group 2, animals receiving propranolol (2 mg/kg) plus epinephrine infusion; group 3, animals receiving phenoxybenzamine (7.5, 2.5 or 1.25 mg/kg) plus epinephrine; and group 4, animals receiving both phenoxybenzamine and propranolol prior to epinephrine infusion. This latter group was subdivided into subgroup A, receiving phenoxybenzamine (7.5 mg/kg) and propranolol (2 mg/kg), subgroup B, receiving phenoxybenzamine (2.5 mg/kg) and propranolol (2 mg/kg), and subgroup C, receiving phenoxybenzamine (1.25 mg/kg) and propranolol (2 mg/kg). In a typical experiment, control measurements were followed by the blocking drug, a 2-hr infusion of epinephrine, a 2-hr period of recovery and a terminal autopsy.

RESULTS. *Group 1 (controls).* In control experiments, epinephrine infusions alone produced a prompt, sharp rise in blood pressure which had fallen below the control value before the end of the 2-hr infusion. Stopping the infusion caused a further fall in blood pressure which showed little tendency to improve during the remainder of the period (fig. 1). Heart rates followed a somewhat similar course (fig. 2) with arrhythmias of varying types and severity appearing in every animal. The electrocardiogram (ECG) was characterized by sinus tachycardia, nodal and ventricular ectopic beats and ventricular tachycardia. Within a few minutes after the infusion began, the R-wave voltage of the ECG was severely depressed and usually remained so throughout the experiment (fig. 3). A sharp increase in hematocrit and a fall in blood pH appeared in every case; pH usually dropped below 7.0 before the end of the infusion (table 1). At autopsy, the pericardial sac yielded from 20 to 50 ml of amber-colored fluid, and cardiac hemorrhage was prominent (table 2). Hemorrhagic areas covered more than 50% of the left ventricular endocardium, sometimes extending entirely through the thickness of the ventricular wall and appearing on the epicardial surface. The right ventricle and both atria were usually involved, although hemorrhage in these areas was generally less extensive.

Group 2 (propranolol). The peak mean blood pressure in group 2 exceeded that of the control group (279 ± 17 *vs.* 234 ± 9 S.E. mm Hg; $P < .05$), probably because of the blocking effect of propranolol on the peripheral vasodilating action of epinephrine. However, blood pressure was sustained no better than in the control group and a severe hypotension occurred on termination of the epinephrine infusion, which resulted in the death of all animals in this group. Although propranolol has been cited for its antiarrhythmic properties (Harris, 1966; Lucchesi *et al.*, 1967), under the conditions of these experiments arrhythmias

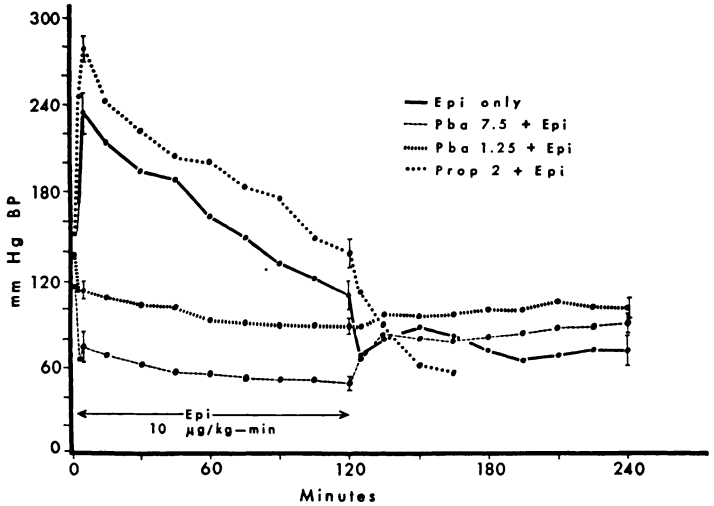

FIG. 1. Mean arterial blood pressure (±S.E.) in dogs receiving a 2-hr i.v. infusion of epinephrine, 10 µg/kg/min. Phenoxybenzamine, 7.5 or 1.25 mg/kg, was given 45 min and propranolol, 2 mg/kg, 10 min prior to the epinephrine infusion. Each line is the mean of five animals. Failure of the dotted line to extend to the 240-min mark indicates death of all animals in the propranolol group. Measurements at 2 hr were made immediately before termination of the epinephrine infusion.

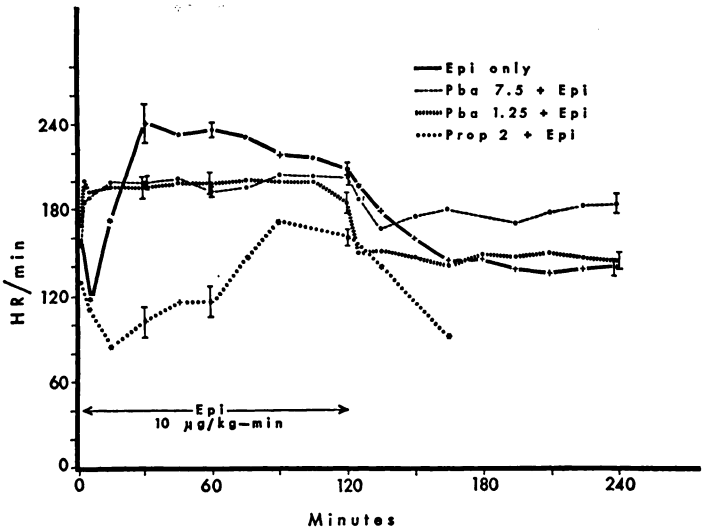

FIG. 2. Heart rate (±S.E.) effects of epinephrine infusion, with and without *alpha* or *beta* adrenergic blockade. Same groups and dosage schedules as figure 1. Because of exclusion of arrhythmias the number of animals at each point is indicated as follows: ●, 5; +, 4; and *, 3.

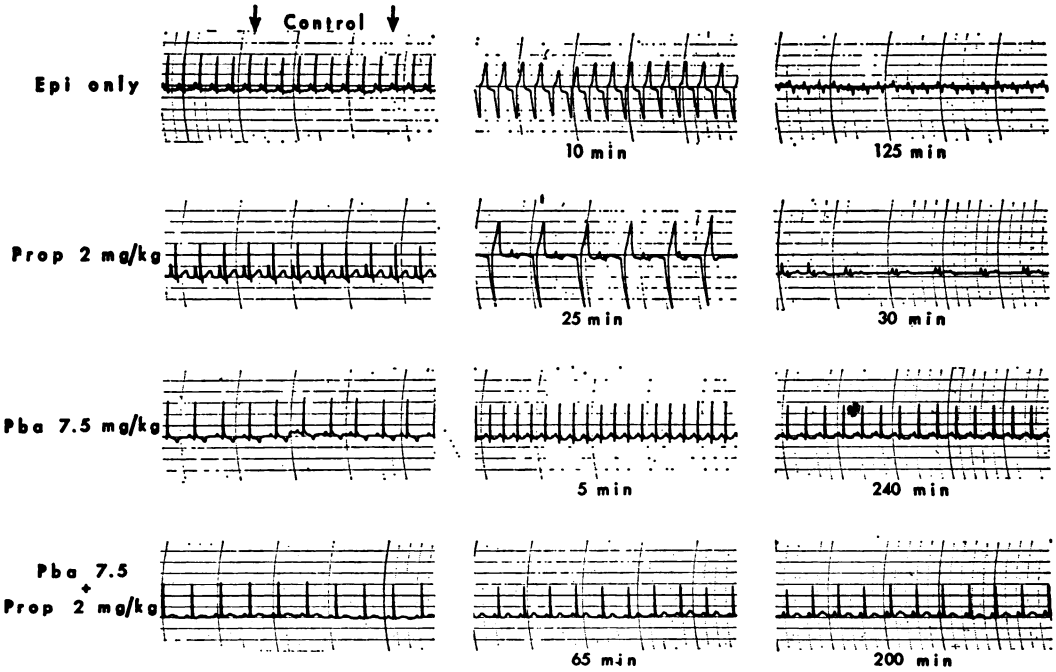

FIG. 3. Representative ECG tracings from dogs in each of the four experimental groups. The left panel in each horizontal row was taken just before the epinephrine infusion; the middle and right panels were taken at the time indicated after the beginning of the infusion. Note the severe arrhythmias and voltage depression in the control and propranolol groups, the tachycardia with *alpha* blockade and the absence of these effects with dual blockade.

TABLE 1

Effects of epinephrine infusion on blood pH and hematocrit with and without dual adrenergic blockade[a]

Pretreatment	Dose	Blood pH			Hematocrit		
		Control	2 hr	4 hr	Control	2 hr	4 hr
	mg/kg						
None		7.37 ± 0.02	6.98 ± 0.03[b]	6.79 ± 0.14[b]	38 ± 2.6	56 ± 5.5[c]	51 ± 6.2
Propranolol	2	7.34 ± 0.02	6.95 ± 0.05[b]		41 ± 2.8	58 ± 7.4[c]	
Phenoxybenzamine	7.5	7.37 ± 0.03	7.24 ± 0.03[c,d]	7.28 ± 0.03	36 ± 0.5	35 ± 0.6[d]	42 ± 0.8[b]
Phenoxybenzamine	2.5	7.33 ± 0.02	7.23 ± 0.09[d]	7.28 ± 0.05	38 ± 1.5	39 ± 2.4[d]	44 ± 2.8
Phenoxybenzamine	1.25	7.36 ± 0.01	7.21 ± 0.02[b,d]	7.24 ± 0.02[b]	35 ± 1.9	45 ± 1.0[b]	46 ± 1.8[b]
Phenoxybenzamine	7.5	7.32 ± 0.03	7.29 ± 0.03[d]	7.33 ± 0.04	38 ± 2.1	37 ± 1.4[d]	38 ± 1.8[b]
+ propranolol	2						
Phenoxybenzamine	2.5	7.36 ± 0.03	7.33 ± 0.05[d]	7.37 ± 0.05	37 ± 2.1	44 ± 2.5	41 ± 1.9
+ propranolol	2						
Phenoxybenzamine	1.25	7.33 ± 0.02	7.24 ± 0.03[c,d]	7.33 ± 0.02	37 ± 0.9	48 ± 2.0[b]	41 ± 2.0
+ propranolol	2						

[a] All dogs received an epinephrine infusion of 10 μg/kg i.v. for 2 hr and were observed for 2 hr more. Tabular values are means ± S.E. for five animals.

[b] Compared to own control, $P < .01$.

[c] Compared to own control, $P < .05$.

[d] Compared to control group at 2 hr, $P < .05$.

TABLE 2

Some toxic effects of epinephrine infusion with and without dual adrenergic blockade[a]

Pretreatment	Dose	Incidence[b] of			ECG R-Wave Voltage[c]	Mortality Rate[d]
		Pericardial effusion[d]	Cardiac hemorrhage[d]	Cardiac arrhythmias[c]		
	mg/kg				*% decrease*	
None		5/5	5/5	5/5	72 ± 4.7	1/5
Propranolol	2	5/5	5/5	5/5	73 ± 5.6	5/5
Phenoxybenzamine	7.5	0/5	4/5	1/5	31 ± 5.7[e]	0/5
Phenoxybenzamine	2.5	0/5	5/5	1/5	32 ± 2.4[e]	0/5
Phenoxybenzamine	1.25	0/5	5/5	3/5	47 ± 7.3[f]	0/5
Phenoxybenzamine	7.5	0/5	0/5	0/5	17 ± 5.1[e]	0/5
+ propranolol	2					
Phenoxybenzamine	2.5	0/5	0/5	0/5	6 ± 1.3[e]	0/5
+ propranolol	2					
Phenoxybenzamine	1.25	0/5	1/5	1/5	1.5 ± 5.6[e]	0/5
+ propranolol	2					

[a] All dogs received an epinephrine infusion of 10 μg/kg i.v. for 120 min and were observed for 120 min more.

[b] Number of positive/total animals.

[c] Data recorded at time of maximum effect or just prior to death. Results are mean of five animals ± S.E.

[d] Data recorded 120 min after end of epinephrine infusion (or at death if earlier).

[e] Compared to nonpretreated group, $P < .01$.

[f] Compared to nonpretreated group, $P < .05$.

occurred in every animal and appeared to be as frequent and as diverse as those in group 1 (fig. 3). Heart rates were somewhat slower in the control state and initially decreased in contrast to the increase seen in group 1. The changes produced in the propranolol-treated animals in blood pH, hematocrit, pericardial fluid, ECG voltage and cardiac hemorrhage were at least equal to those seen in the control group (tables 1 and 2).

Group 3 (phenoxybenzamine). In this study the lowest dose of phenoxybenzamine employed, 1.25 mg/kg, is near the minimum epinephrine-reversing dose, while the highest dose, 7.5 mg/kg, reduces the pressor response to norepinephrine by 70% or more (unpublished data). All doses resulted in a hypotensive response to epinephrine infusions, with the highest dose producing the lowest blood pressure (fig. 1). Heart rates rapidly increased in all cases to a maximum of approximately 200 beats/min during the epinephrine infusion, with more persistent tachycardia at the highest dose. Electrocardiographic voltage depression was about one-half of that seen in control animals (table 2). Intermittent arrhythmias were recorded in one animal at the high dose and in three at the low dose. Blood pH and hematocrit changes due to epinephrine were less than in controls at the two higher dose levels of phenoxybenzamine (table 1). No excess pericardial fluid was found in any phenoxybenzamine-treated animal. Cardiac hemorrhage was present in all animals receiving the two lower doses of phenoxybenzamine and in four out of five receiving the high dose. Although no attempt was made at quantitation, it appeared that the degree and extent of hemorrhage was somewhat less than in the control group.

Group 4 (dual adrenergic blockade). In subgroup A, which received the combination of phenoxybenzamine (7.5 mg/kg) plus propranolol (2 mg/kg), blood pressure rose only briefly and was stable during the remainder of the epinephrine infusion (fig. 4). Furthermore, when epinephrine was abruptly discontinued, there was no change in blood pressure. In subgroup B, which received 2.5 mg/kg of phenoxybenzamine plus 2 mg/kg of propranolol, mean blood pressure rose from a control of 119 ± 9.5 to a peak of 156 ± 13.1 mm Hg and was still somewhat above the control level when the infusion ended. Subgroup C, receiving 1.25 mg/kg of phenoxybenzamine plus 2 mg/kg of propranolol, gave the greatest pressor response, increasing from 120 ± 8 to a peak of 200 ± 7.7 mm Hg. During the latter portion of the epinephrine infusion, blood pressure was stable at 35 to 40 mm Hg above control; *e.g.*, after 120 min of infusion, blood pressure was 155 ± 8.2 *vs.* 120 ± 8 mm Hg ($P < .05$). The outstanding characteristic of all subgroups was the failure of blood pressure to fall below control levels, other than briefly,

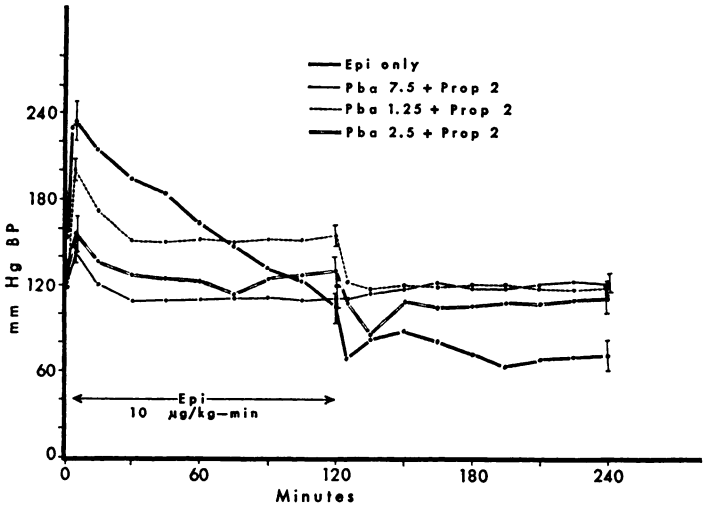

FIG. 4. Mean blood pressure response to epinephrine infusion with and without dual adrenergic blockade. Details as in figure 1.

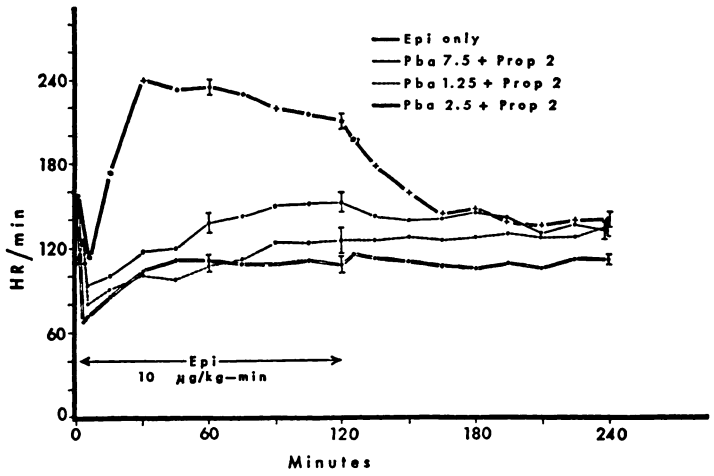

FIG. 5. Heart rate changes induced by epinephrine infusion with and without dual adrenergic blockade. Details as in figures 1 and 2.

on termination of the epinephrine infusion. Heart rates fell with the start of the infusion but soon began to recover and were generally stable for the remainder of the experimental period (fig. 5). At the 7.5- and 2.5-mg/kg doses, all of the other recorded effects of epinephrine infusion were virtually eliminated (tables 1 and 2). With the 1.25-mg/kg dose there was slight cardiac hemorrhage and a few ectopic beats in one animal, indicating that this was near the minimum dose of phenoxybenzamine in combination with propranolol to protect against the toxic effects of epinephrine.

DISCUSSION. Previous workers have tried to block the hemorrhage effect of catecholamines by using *alpha* blockade. Using 20 mg/kg of Dibenamine, Waters and de Suto-Nagy (1950b) were apparently able to prevent myocardial hemorrhage produced by acute injections of epinephrine. Maling *et al.* (1964) infused smaller amounts of norepinephrine and claimed protection by 5 mg/kg of phenoxybenzamine. However, under the conditions of our study, involving three dose levels of phenoxybenzamine, we were unable to eliminate cardiac hemorrhage. Our high dose of phenoxybenzamine produced a questionable reduction in myocardial hemorrhage and the two lower doses had no apparent effect. Thus, at none of the dose levels of group 3 was hemorrhage eliminated. Conversely, propranolol increased the degree and severity of cardiac hemorrhage in all animals studied. In view of the weak suppressive action of phenoxybenzamine and the increase in hemorrhage with propranolol, it was somewhat surprising to find that the combination of propranolol plus phenoxybenzamine (2.5 or 7.5 mg/kg) completely eliminated myocardial hemorrhage. Even the low dose of phenoxybenzamine, 1.25 mg/kg, prevented hemorrhage in four of five animals.

The ability of dual adrenergic blockade to eliminate myocardial hemorrhage even in the presence of a significant pressor effect would seem to rule out the suggestion of Mazzella *et al.* (1964) and Waters and de Suto-Nagy (1950b) that hemorrhage was due to the rise of blood pressure. The evidence against such a view may be summarized as follows. 1) Workers claiming elimination of cardiac hemorrhage through use of *alpha* adrenergic blockade have used doses considerably above the minimal epinephrine-blocking dose. 2) No one using minimal *alpha* blockade has claimed prevention of cardiac hemorrhage. 3) The atria, with only slight pressure changes, are subjected to hemorrhage almost as frequently as the ventricles. 4) A significant rise of aortic pressure in the presence of dual blockade, which is better sustained than in controls, does not cause hemorrhage.

The postulation by Szakacs and Cannon (1958) that excessive vagal tone may be the primary factor in cardiac hemorrhage was negated by Nash and Carter (1967), who

found no decrease in hemorrhage in vagotomized dogs. Szakacs and Mehlman (1960) implicated ventricular tachycardia on the basis of stasis of capillary blood flow during the contractile phase; however, in the present work, propranolol prevented ventricular tachycardia but did not reduce myocardial hemorrhage. Gauer and Henry (1964) found that a catheter in the left ventricle would record systolic peak pressure far above systolic aortic pressure during injections of epinephrine, and they suggested that myocardial hemorrhage resulted from squeezing by ventricular walls on an empty chamber. If this were the case, *beta* blockade by propranolol should have reduced or prevented the hemorrhage along with the reduction in contractile force response to epinephrine. In the present study, propranolol increased rather than decreased cardiac hemorrhage. Furthermore, the atrial muscle was also subjected to hemorrhagic damage, and there is no similar pressure or squeezing factor involved.

Dual adrenergic blockade not only prevented cardiac hemorrhage but also eliminated or markedly reduced pericardial effusion, cardiac arrhythmias, hematocrit increases, acidemia and ECG voltage depression. Heart rates showed only a small fluctuation and blood pressure was quite stable when epinephrine infusion was discontinued. By reducing the dose of phenoxybenzamine to 1.25 mg/kg in combination with propranolol, it was possible to achieve a marked rise in blood pressure with epinephrine at a cost of an occasional ectopic beat and a few faint hemorrhagic streaks in one animal. The intermediate dose combination permitted a moderate blood pressure increase to epinephrine with no hemorrhage and no ectopic beats.

The ability of the *beta* blocking agent, pronethalol, to antagonize the epinephrine-reversing action of phenoxybenzamine has been documented by Goncalves Moreira and Osswald (1965) and Gulati *et al.* (1965), and more recently Sharma (1966) and Olivares *et al.* (1967) have obtained similar results with propranolol. In the present study, the pressor response to epinephrine obtained in the presence of phenoxybenzamine was undoubtedly related to this same antagonism between phenoxybenzamine and propranolol. However, an important point is raised by the finding that the two agents do not show antagonism to each other on other effects of epinephrine but rather appear to summate so that toxic actions of epinephrine are eliminated. The possibility exists that the *alpha* and *beta* blockers are antagonistic with regard to vascular effects but reinforce each other on metabolic effects. Precedence for such a concept may be found in the action of *alpha* and *beta* receptors in the gut where both subserve similar effects (Ahlquist and Levy, 1959). This point deserves further study.

These findings may have some relevance to clinical problems. For example, the very encouraging results (Pritchard and Ross, 1966; Crago *et al.*, 1967; Ross *et al.*, 1967) with the use of dual blockade in the preoperative and operative treatment of patients with pheochromocytoma may be based, in part, on suppression of some of the toxic and metabolic effects of high levels of circulating catecholamines, in addition to limiting wide swings in blood pressure.

Dual adrenergic blockade clearly has the capacity to eliminate myocardial hemorrhage resulting from a 2-hr infusion of epinephrine (10 μg/kg/min) in dogs. Additional protective effects of dual blockade include the absence of marked shifts in blood pressure when the pressor agent was discontinued, smoother control of blood pressure and heart rate and elimination or marked reduction of other toxic effects of epinephrine. Adjustment of the ratio of *alpha* to *beta* blocking agents indicates that a considerable degree of pressor response to epinephrine may be retained without incurring toxic signs.

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