Guanethidine and bretylium are two relatively new drugs used in the treatment of hypertension. Both of these agents may produce a triphasic effect on arterial pressure when administered intravenously; the initial response is usually an abrupt fall in arterial pressure lasting less than 5 minutes, followed by a more sustained pressor effect which may persist for 30 minutes to 2 hours, depending upon the dose. The third phase is a moderate depressor effect which may last for several days. The transient pressor effect produced by guanethidine and bretylium is accompanied by marked positive inotropic and chronotropic effects. It has been suggested that guanethidine increases arterial pressure and systemic vascular resistance by suddenly releasing catecholamines and, in support of this suggestion, guanethidine has been shown to reduce myocardial amine content and to have its pressor effect reduced, abolished, or reversed by pretreatment with phentolamine or reserpine. Bretylium, on the other hand, is reported to have no effect on tissue catecholamine content.

Observations in heart-lung preparations made from normal and reserpine-pretreated dogs suggested that both guanethidine and bretylium produce sudden myocardial catecholamine release and that this release may be largely responsible for the initial positive inotropic and chronotropic effects produced by these two drugs in the isolated heart. These observations in the heart-lung preparation suggested that release of catecholamines from the myocardium itself may be a major factor in producing the pressor, inotropic, and chronotropic effects of guanethidine and bretylium in the intact dog.

Cooper and associates have recently developed an operation resulting in total cardiac denervation and cardiac catecholamine depletion in an otherwise healthy dog. A comparison of the effects produced by the intravenous administration of guanethidine or bretylium in normal and cardiac-denervated dogs provided the opportunity to determine the contribution of the release of catecholamines from the myocardium alone to the acute circulatory effects of these drugs as seen in the intact animal.

Methods

Two types of experiments were performed on mongrel dogs, weighing 10 to 21 Kg., which were anesthetized with 100 mg./Kg. chloralose administered intravenously. In the first type of experiment carried out on control and cardiac-denervated dogs, a thoracotomy was performed following the institution of positive pressure breathing. Right ventricular contractile force was measured with a Walton-Brodie strain-gauge arch. Systolic arterial pressure was recorded through a catheter in the femoral artery with a Statham P23A transducer. In the second series of experiments, cardiac outputs were measured in control and cardiac-denervated closed-chest dogs, utilizing the indicator-dilution technique. Indocyanine dye was injected through a Cournand catheter, the tip of which was positioned in the right atrium, and arterial blood was withdrawn through a catheter the tip of which was located in the arch of the aorta and pulled through a cuvette densitometer by means of a constant withdrawal syringe. Cardiac outputs were measured at 4 and 2 minutes before and at 1, 2, 4, and 10 minutes following injection of the drug under study.

Cardiac denervation was performed as described previously. All of the denervated dogs were studied at least seven days after operation, after the lapse of a time interval which is sufficient for maximal myocardial catecholamine depletion to occur. At the time of study, the dogs appeared to be in good condition and had regained their predenervation weight. In each type of experiment, only one drug, either guanethidine or bretylium, was administered intravenously. In experiments in which right ventricular contractile
force was measured, one of these drugs was given in repeated single injections in doses ranging from 0.1 mg. to 10.0 mg./Kg., with sufficient time allowed between doses for all parameters to return to control values. In experiments in which cardiac outputs were measured, only a single injection of 10 mg./Kg. of either guanethidium or bretylium was made. Different control dogs were utilized for each drug, but the same group of denervated dogs was employed for both drugs with at least 10 days permitted to elapse between studies on the same denervated dog.

Results

PROOF OF CARDIAC DENERVATION

The completeness of cardiac denervation and myocardial catecholamine depletion was tested pharmacologically in each cardiac-denervated dog. It has been shown that complete cardiac denervation with resultant myocardial catecholamine depletion is associated with a loss of the positive inotropic and chronotropic responses to 60 /g./Kg. of tyramine, and of the reflex negative chronotropic responses to 0.25 /g./Kg. norepinephrine, which are seen in normal dogs (figs. 1 and 2). It is evident in figures 1 and 2 that the control heart rates were lower (110 and 140 beats/min.) in the denervated, amine-depleted dogs than in the normal dogs (150 and 160 beats/min.). This was a consistent finding and correlates with the slower heart rates seen in the reserpine-pretreated (myocardial amine-depleted) heart-lung preparation. The administration of 120 /g./Kg. of tyramine to the cardiac-denervated dogs produced a pressor response without the associated positive inotropic and chronotropic effects that are seen in the normal dogs. These latter pressor responses to tyramine occurring without cardiac effects in the cardiac-denervated dog are presumably the result of the release of catecholamines from tissues other than the heart. Each cardiac-denervated dog employed in this study demonstrated the responses to tyramine and norepinephrine illustrated in figures 1 and 2.

GUANETHIDINE

Inotropic and Chronotropic Effects in Open-Chest Dogs

In three normal open-chest dogs, guanethidine produce a significant augmentation of
right ventricular contractile force and heart rate. These effects began within 30 seconds after injection, reached a peak within 1 minute, and with a dose of 10.0 mg./Kg., persisted for approximately 35 minutes. In contrast, in four cardiac-denervated open-chest dogs, guanethidine had no discernible effect on right ventricular contractile force or heart rate in doses up to 0.3 mg./Kg., but doses of 1.0 to 10.0 mg./Kg. produced a slight decrease (3 to 12 per cent) in ventricular contractile force in two of four dogs, and a marked decrease (40 per cent) in one dog; the latter dog had received only a single injection of 10.0 mg./Kg. of guanethidine. No changes in myocardial contractile force occurred with these doses in the fourth cardiac-denervated dog (fig. 3). In six normal open-chest dogs, the increase in heart rate produced by 10 mg./Kg. of guanethidine ranged from 25 to 105 per cent above control levels, whereas in four cardiac-denervated dogs, the heart rate increased from 0 to 20 per cent (fig. 4).

**Arterial Pressure in Closed-Chest Dogs**

Immediately following the injection of 10 mg./Kg. of guanethidine, mean arterial pressure decreased to a similar extent in both the normal and the cardiac-denervated closed-chest dogs. In the four normal closed-chest dogs, guanethidine then produced a maximum increase in mean arterial pressure which ranged from 18 to 52 per cent above the control values. In contrast, in four cardiac-denervated closed-chest dogs studied, this dose of guanethidine increased mean arterial pressure by only 5 to 20 per cent above control levels (fig. 5).

**Cardiac Output in Closed-Chest Dogs**

Guanethidine, 10 mg./Kg., administered to four normal, closed-chest dogs, increased cardiac output to peak levels which ranged from 50 to 280 per cent above control. In contrast, in three cardiac-denervated closed-chest dogs, the peak increments in output produced by this dose of guanethidine ranged between 20 and 55 per cent (fig. 6). The only increase in mean arterial pressure produced by guanethidine in a normal dog which was in the same range as that which was observed in the cardiac-denervated dogs occurred in dog no. 62. It can be seen in figures 5 and 6 that this particular dog also had the smallest increment in cardiac output produced by guanethidine in any of the normal dogs, and that this change in cardiac output was in the same range observed in the cardiac-denervated dogs.

**BRETYLIUM**

**Inotropic and Chronotropic Effects in Open-Chest Dogs**

Bretylium, in doses ranging from 0.3 to 10.0 mg./Kg., produced a significant increase
Effects of guanethidine, 10 mg./Kg. I.V., on mean arterial pressure in normal and cardiac-denervated dogs.

These effects had a time course similar to those observed for guanethidine. In three cardiac-denervated open-chest dogs, identical doses of bretylium resulted in increases in contractile force which were essentially the same in degree as those produced in the normal dogs (fig. 3). However, the positive chronotropic effect of bretylium observed in seven normal dogs (5 to 100 per cent above control levels) was reversed in the cardiac-denervated dogs in which the heart rate fell 17 to 25 per cent below control levels in three dogs and remained unchanged in the fourth dog (fig. 4).

Arterial Pressure in Closed-Chest Dogs

The initial fall in mean arterial pressure produced by 10 mg./Kg. of bretylium was 1 to 5 per cent of control values in three normal dogs and 4, 18, and 25 per cent of control values in three cardiac-denervated dogs. In the three normal closed-chest dogs, bretylium produced a maximum increase in mean arterial pressure of 18 to 40 per cent above control levels. In two cardiac-denervated closed-chest dogs, this maximum increment was 16 and 48 per cent, whereas in a third dog only a depressor effect was observed. Thus, the pressure response to bretylium in the normal and cardiac denervated dogs were not dissimilar (fig. 7).

Cardiac Output in Closed-Chest Dogs

The peak increases in cardiac output produced by bretylium in four normal closed-chest dogs during the 10 minutes following injection ranged from 25 to 53 per cent above control levels. In three cardiac-denervated dogs, bretylium increased cardiac output to peaks of only 8, 18, and 24 per cent above control levels (fig. 8). Although there was some overlap in the output responses of the two groups of dogs to bretylium, there was a tendency for the cardiac output to rise less in the denervated dogs.

Discussion

In order to define the mechanism of action of drugs which act upon the cardiovascular system, it is essential to separate the cardiac from the peripheral vascular effects. Furthermore, in the study of drugs, the action of which may involve the release of catecholamines, it is also helpful to compare effects in normal and catecholamine-depleted states, since the acute effects of these drugs in the normal animal may vary from their long-term effects. With this type of experimental design, it is possible to distinguish the effects of a drug resulting from the release of catecholamines from those actions unrelated to the release of amines or occurring only in the amine-depleted state. This approach is
GUANETHIDINE AND BRETYLIUM

facilitated by the use of a preparation in which the catecholamine depletion can be confined to a single organ, such as the heart. Thus, the chronic cardiac-denervated preparation with resultant myocardial catecholamine depletion, employed in the present investigation, provided the opportunity to determine the contribution of myocardial catecholamine release to the acute circulatory effects of guanethidine and bretylium as seen in the intact dog and to observe the effects of these drugs on the aminedeplated heart, in an otherwise intact dog.

In these experiments, it was shown that the acute effects of guanethidine on cardiac output, myocardial contractile force, arterial pressure, and heart rate in the normal dog could be almost completely prevented by previous cardiac denervation with resultant depletion of only myocardial catecholamines. Thus, it would appear that in the dose range explored (0.1 mg./Kg. to 10.0 mg./Kg.), many of the acute circulatory effects of guanethidine are primarily the result of sudden cardiac catecholamine release. In all seven closed-chest animals given guanethidine, the relative elevation of cardiac output exceeded the relative rise in arterial pressure, i.e., systemic vascular resistance declined. It thus seems probable that the pressor effect of guanethidine in intact animals results primarily from the increase in cardiac output rather than from any vasoconstriction. The intravenous administration of guanethidine also raises arterial pressure and heart rate in man,11 and it is probable that these effects are also related to the release of myocardial catecholamines. Guanethidine has also been reported to release catecholamines from vessel walls and the spleen;12 this effect may account for the small increase in arterial pressure, cardiac output, and heart rate produced by guanethidine in the cardiac-denervated dogs.

Early studies with bretylium did not show that this drug depleted tissues of their catecholamine stores.5 However, it was suggested, and subsequently shown,13 that this drug is capable of releasing catecholamines from the heart. The results of the present studies with bretylium indicate that the increases in myocardial contractile force and arterial pressure produced by this drug are not dependent upon release of catecholamines from the myocardium alone, since the augmentation of these parameters produced by bretylium in the cardiac-denervated dogs was almost the same as in the normal dogs. These experiments do not exclude a contribution to these effects from amines released from tissues other than the heart. In the cardiac-denervated dogs there was a reversal of the positive chronotropic effects produced by bretylium in the normal dogs (fig. 4) and, in addition, there was a tendency for the increments in cardiac output to be less prominent in the cardiac-denervated dogs than in the normal dogs. These data suggest that the release of myocardial catecholamines plays a definite

FIGURE 7
Effects of bretylium, 10 mg./Kg. I.V., on mean arterial pressure in normal and cardiac-denervated dogs.

FIGURE 8
Effects of bretylium, 10 mg./Kg. I.V., on cardiac output in normal and cardiac-denervated dogs. Changes are expressed as a per cent of the mean of two control cardiac outputs measured three minutes and one minute prior to drug injection.
but limited role in the acute hemodynamic effects of bretylium. The decrease in myocardial contractile force produced by large doses of guanethidine in the amine-depleted heart indicates that, in addition to producing myocardial catecholamine release in the normal dog, this drug may, in large doses, also have a direct negative inotropic effect in the amine-depleted heart. Similarly, the positive inotropic effect and the negative chronotropic effect produced by bretylium in the amine-depleted heart suggest that these are also direct effects, not dependent upon catecholamine release.

Summary
The acute effects of guanethidine and bretylium on myocardial contractile force, heart rate, mean arterial pressure, and cardiac output were studied in normal dogs and cardiac-denervated, myocardial catecholamine-depleted dogs. Right ventricular contractile force was measured by means of a Walton-Brodie strain-gauge arch. Cardiac output was measured by the dye-dilution technique.

In normal dogs, guanethidine produced marked increases of myocardial contractile force, heart rate, cardiac output, and arterial pressure. In the cardiac-denervated dogs, guanethidine produced a small decrease in myocardial contractile force and a small increase in heart rate; the cardiac output and pressor responses were also markedly reduced. Thus, it appears that sudden release of myocardial catecholamines is largely responsible for the acute circulatory effects of guanethidine.

In normal dogs, bretylium increased myocardial contractile force, heart rate, cardiac output, and arterial pressure. In cardiac-denervated dogs, the increase in contractile force produced by bretylium was essentially unchanged from the normal, but the heart rate was decreased, and the cardiac output response appeared slightly reduced. These data suggest that myocardial catecholamine release plays a limited but definite role in the acute circulatory effects of bretylium.

The negative inotropic effect of guanethidine and the negative chronotropic effect of bretylium in the denervated, amine-depleted heart suggest that these responses are direct effects of these drugs which are manifest only in the amine-depleted heart.

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