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THE EFFECT OF ADRENERGIC NEURONE BLOCKADE ON THE MYOCARDIAL CIRCULATION

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Although reflexes to the coronary circulation from the heart and blood vessels, and from extra-cardiac visceral structures, certainly exist and are possibly implicated in initiating anginal attacks in man, a study of the relevant nervous pathways has generally involved extensive cannulation and dissection of the coronary arteries. In a recent monograph, Kaverina (1965) has made a study of reflexes arising as a result of changes in pressure in the carotid sinus, and of stimulation of pericardial receptors and of afferent fibres in the tibial nerve. The results were interpreted as demonstrating the existence of coronary vasoconstrictor reflexes, the efferent arc being the cardiac sympathetic nerves. In other, less traumatic, experiments with extra-cardiac stimuli however, changes in coronary flow paralleled changes in heart rate and blood pressure and there was little evidence to suggest that flow was significantly influenced through nervous pathways to the vessels themselves (see Gregg & Fisher, 1963). Using adrenergic neurone blocking drugs it should be possible to prevent the action of the efferent adrenergic nerves to the myocardial vessels without affecting the function either of afferent fibres, or of efferent cholinergic fibres running in the vagus or in the cardiac sympathetic nerves. This initial study describes the effects of adrenergic neurone blockade on myocardial haemodynamics in dogs, using a heat-exchange method which involves very little operative interference with the myocardial vessels. In view of the observation of Grayson & Mendel (1961) that myocardial blood flow is increased during vagal stimulation in atropinized rabbits, experiments were also performed in dogs to determine whether this flow increase involved adrenergic neurones.

METHODS

The effect of adrenergic neurone blockade, intravenous bretylium tosylate, 10 mg/kg (Boura & Green, 1959) or bethanidine sulphate, 3 mg/kg (Boura & Green, 1963), on blood pressure, heart rate, left myocardial blood flow and vascular resistance and on myocardial metabolic heat production was studied in 25 mongrel dogs weighing between 7 and 11 kg. The dogs were anaesthetized with sodium pentobarbitone (40 mg/kg, intraperitoneally). Blood pressure was measured from a polyethylene cannula in the left femoral artery using a mercury manometer or a Shillingford-Muller transducer. Left myocardial blood flow was measured using the heated thermocouple method of Grayson & Mendel (1961), the cold junction (mounted in a polyethylene tube) being inserted down

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the left antebrachial artery as far as the aortic arch. The thermocouples were inserted into the left myocardium in the area mainly supplied by the anterior ventricular branch of the left descending coronary artery (see Blair, 1961). Myocardial temperature was recorded from these themocouples on photographic paper (Ilford GP5, width 120 mm) using a Cambridge recording camera, at a paper speed of 0.2 mm/sec. These records were also analysed to obtain indications of myocardial metabolic heat production (" corrected temperature ") as described by Dosekun, Grayson & Mendel, 1960. Full details of the operative procedure, analysis of results and validity of the method, have been described in previous papers (Parratt, 1964 ; Grayson & Parratt, 1966).

In 14 experiments the effects of adrenaline on the myocardial circulation were studied before, and from 30 to 180 min after, adrenergic neurone blockade. The adrenaline was given by infusion, using a continuous slow-injection apparatus delivering 0.5 ml./min, through a polyethylene cannula in the left femoral vein.

A total of 24 experiments were also performed in six dogs injected with atropine sulphate (1 mg/kg intravenously as base) in which the peripheral ends of the right and left vagus nerves were stimulated before and after adrenergic neurone blockade with bretylium tosylate or bethanidine sulphate. The common vagus trunks were separated in the neck and the peripheral ends stimulated using a Palmer electronic square-wave stimulator (usually 7 v, 10–50/sec, 1 msec).

RESULTS

The effect of bretylium on the myocardial circulation

Bretylium was injected intravenously over a period of 2 min and it was immediately at the end of this period that the effects of myocardial blood flow and heart rate were most pronounced. Myocardial flow was increased by a mean of 62% (range 13–82%) and heart rate by 9% (15 beats/min ; range 0–33 beats/min) at the end of the injection. Blood pressure usually fell immediately after the injection by 20–30 mm Hg from the pre-injection level of 139 mm Hg. As this decrease in blood pressure coincided with the maximal increase in myocardial blood flow, this indicates a very marked reduction in myocardial vascular resistance sometimes amounting to as much as 43%. Thereafter myocardial blood flow and heart rate returned towards pre-injection levels but blood pressure increased to reach a peak 5 min from the start of the injection. A typical result is illustrated in Fig. 1 and the results for the whole series are summarized in Table 1. It will be observed that when adrenergic neurone blockade is complete, systemic blood pressure, heart rate and myocardial blood flow are all reduced below the initial pre-injection levels while vascular resistance within the myocardium is increased.

Bretylium increased " corrected temperature " in eight out of the 11 experiments in which it was measured and decreased it in two. The effect was gradual, the mean increase at the end of 30 min being 0.04° C (range −0.17 to +0.35° C) and at 1 hr +0.07° C (range −0.11 to +0.44° C). It would appear, therefore, that when adrenergic neurone blockade to the myocardium is complete there is a clear and significant increase in left myocardial metabolic heat production.

The effect of bethanidine on the myocardial circulation

There was usually a brief fall in blood pressure of from 6–19 mm Hg when bethanidine was injected intravenously, but within 2 min of the completion of the injection blood pressure began to rise sharply (Fig. 2). The maximum rise in arterial blood pressure was 39 mm Hg (range 0–72 mm Hg ; S.E. of mean ±4.7 mm Hg) and this was usually reached 5 to 15 min after the injection. The pressure remained elevated for up to 2 hr

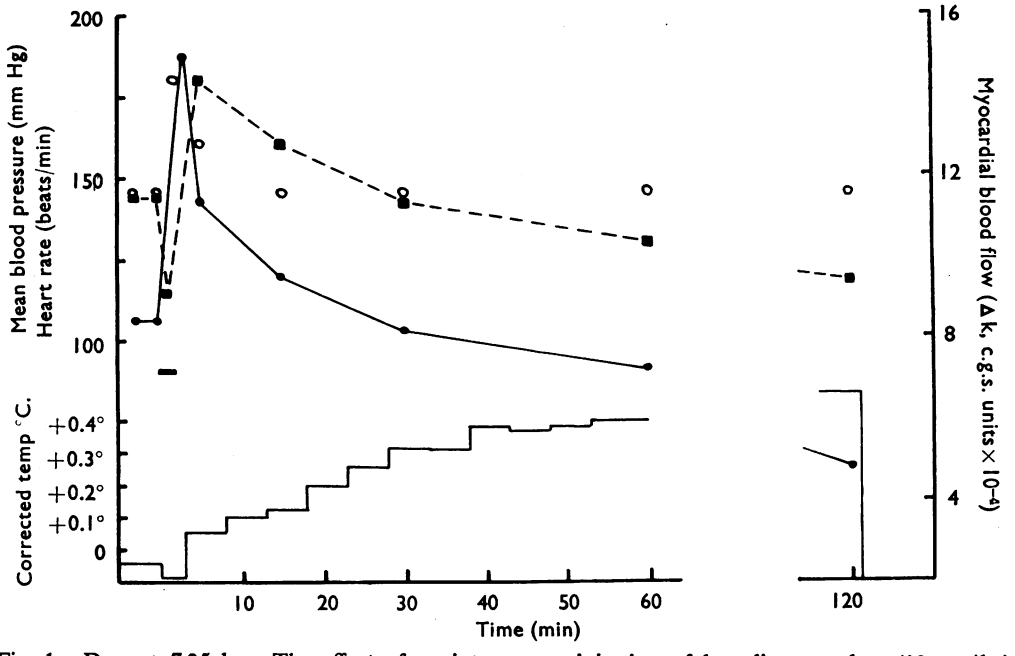

Fig. 1. Dog ♂ 7.25 kg. The effect of an intravenous injection of bretylium tosylate (10 mg/kg), on arterial blood pressure (■ - - - ■), heart rate (○), left myocardial blood flow (●——●) and left myocardial metabolic heat production (open columns).

TABLE 1

THE EFFECT OF SINGLE INTRAVENOUS INJECTION OF BRETYLIUM TOSYLATE (10 MG/KG) ON MEAN SYSTEMIC BLOOD PRESSURE, HEART RATE, LEFT MYOCARDIAL BLOOD FLOW AND CALCULATED MYOCARDIAL VASCULAR RESISTANCE IN DOGS

Results expressed as mean percentage change from the pre-injection level ±S.E.

	Time after injection (min)						
Pre-injection values	1–2	5	10	15	30	60	90
Blood pressure 139±9 mm Hg	−20±4	+21·3±4	+5±1·5	+9·4±3	−5±1·7	−13±2	−15·6±3
Heart rate 164±5 beats/min	+9±2·4	−2·2±1	−7·5±2	−5·8±4	−13±3	−11·7±2·6	−16·3±3
Myocardial blood flow (Δk) 4·5±0·6×10⁻⁴ c.g.s. units	+62±5·2	+35±3	+2±1·6	+1·2±2·9	−14·6±4·3	−18±4·3	−28±6·2
Myocardial vascular resistance 36±4 units	−26±5	−7·2±2·7	+3·3±3	+9±3·7	+18·3±6	+17·4±8	+22·2±9

(Table 2 and Fig. 2). Substantial elevations in heart rate were also observed (maximum increase 37 beats/min; range 0–87 beats/min; S.E. of mean ±4.1) and, like the blood pressure, these were maintained for up to 2 hr. Despite the very marked increase in systemic blood pressure, reflex vagal bradycardia was seen on only a few occasions and, when it did occur, it was relatively short-lived.

TABLE 2

THE EFFECT OF A SINGLE INTRAVENOUS INJECTION OF BETHANIDINE SULPHATE (3 MG/KG) ON MEAN SYSTEMIC BLOOD PRESSURE, HEART RATE, LEFT MYOCARDIAL BLOOD FLOW AND CALCULATED MYOCARDIAL VASCULAR RESISTANCE IN DOGS

Results expressed as mean percentage change from the pre-injection level±S.E.

Pre-injection values	Time after injection (min)				
	5	10	30	60	120
Blood pressure 126±3 mmHg	+27±4·2	+29±5	+26±8·1	+22±9	+32±10
Heart rate 157±6 beats/min	+20±4	+19±4·7	+19±3·7	+16±2·7	+12±3·5
Myocardial blood flow (Δ k) $5{\cdot}2\pm1{\cdot}1\times10^{-4}$ c.g.s. units	+36±8·9	+25±10·6	+29·6±9·7	+30±11·5	+19±5·8
Myocardial vascular resistance 29±5·2 units	−4±2·5	+5·7±1·9	−2·1±2·1	−4·1±3·6	+8·5±7·4

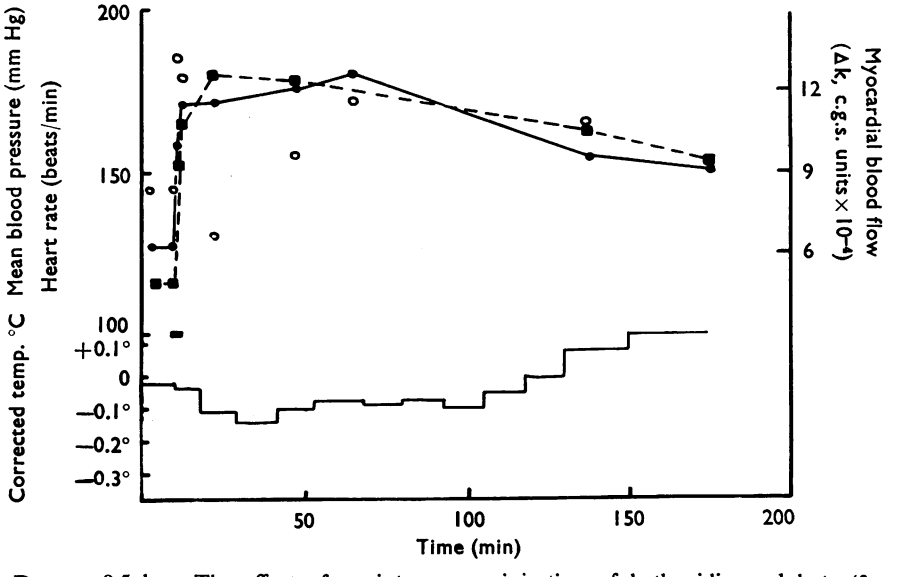

Fig. 2. Dog ♂ 8.5 kg. The effect of an intravenous injection of bethanidine sulphate (3 mg/kg) on arterial blood pressure (■ - - - ■), heart rate (○), left myocardial blood flow (● —— ●) and left myocardial metabolic heat production (open columns).

There were no clear changes in " corrected temperature " until 2 hr after the injection when, in the four experiments in which it was analysed, it was raised by a mean of 0.17° C (range 0.15 to 0.29° C). One hour after the bethanidine injection it was raised in three animals, decreased in five and unchanged in the rest. No consistent changes in " corrected temperature " were observed in animals under pentobarbitone sodium anaesthesia which were left for 2 hr without either bethanidine or bretylium. The increase in " corrected temperature " at 2 hr after bethanidine therefore probably reflects a definite increase in myocardial metabolic heat production and not a general change in body metabolism.

The effect of adrenaline on the myocardial circulation before and after adrenergic neurone blockade

The results are summarized in Table 3. The effects in control dogs were similar to those previously described using the same technique (Parratt, 1965): increased blood flow and pressure and decreased myocardial vascular resistance. Vagotomy, as one would expect, potentiated the effects on blood pressure but the effects on myocardial

TABLE 3

THE EFFECT OF INTRAVENOUS INFUSIONS OF ADRENALINE ON BLOOD PRESSURE, HEART RATE, LEFT MYOCARDIAL BLOOD FLOW AND CALCULATED LEFT MYOCARDIAL VASCULAR RESISTANCE BEFORE, AND AFTER, ADRENERGIC NEURONE BLOCKADE WITH BRETYLIUM TOSYLATE (10 MG/KG).

Values are the means of the maximal response during the ten-minute infusion period, expressed as a percentage change from pre-infusion levels. The range is in brackets.

* After bilateral vagotomy.

Adrenaline (μg/kg/min)	Expts. (no.)	Before bretylium				After bretylium			
		bp	hr	mbf	mvr	bp	hr	mbf	mvr
0·25	5	+12 (0–21)	−5 (0–−7)	+32 (30–34)	−16 (−7–−24)	+64 (57–71)	−27 (−17–−36)	+165 (160–182)	−39 (−37–−40)
*0·25	5	+36 (24–54)	−2 (0–−6)	+19 (15–27)	+6 (−3–+16)	+73 (70–85)	+12 (9–15)	+122 (87–180)	−18 (−6–−37)
0·5	4	+23 (0–29)	−5 (0–−10)	+94 (32–246)	−29 (−11–−73)	+81 (57–94)	−25 (−2–−40)	+260 (73–483)	−41 (−5–−69)

blood flow were somewhat reduced. After bretylium the effects on blood pressure and on myocardial flow were potentiated about two to five times. A typical result is illustrated in Fig. 3.

The effect of vagal nerve stimulation on the myocardial circulation in atropinized dogs

Stimulation of the peripheral end of the vagus nerve in 22 out of 24 experiments on six atropinized dogs resulted in increased myocardial blood flow, a typical example being illustrated in Fig. 4. In general, there were no marked differences between right or left vagal stimulation. In the 10 experiments where the right vagus was stimulated, the mean blood flow increase was 31% (range 6–79%) and the mean systemic blood pressure increased by 11% (range 2–22 mm Hg). In five of these experiments there was no change in heart rate and in the other five it increased by a mean of 8% (range 2–20 beats/min). The corresponding figures for left vagal nerve stimulation were, for myocardial blood flow, +30% (range 10–60%) and for mean systemic blood pressure, +11% (range 6–20 mm Hg). Increases in heart rate were observed in only two experiments and were slight (+6%). These effects on blood flow, blood pressure and heart rate, which occurred when the nerves were stimulated, were either abolished or greatly reduced after adrenergic neurone blockade.

In one atropinized dog, however, unusually large flow increases (184 and 240%) were observed when the peripheral end of the left vagus nerve was stimulated and these were accompanied by marked increases in blood pressure (94 and 82 mm Hg respectively),

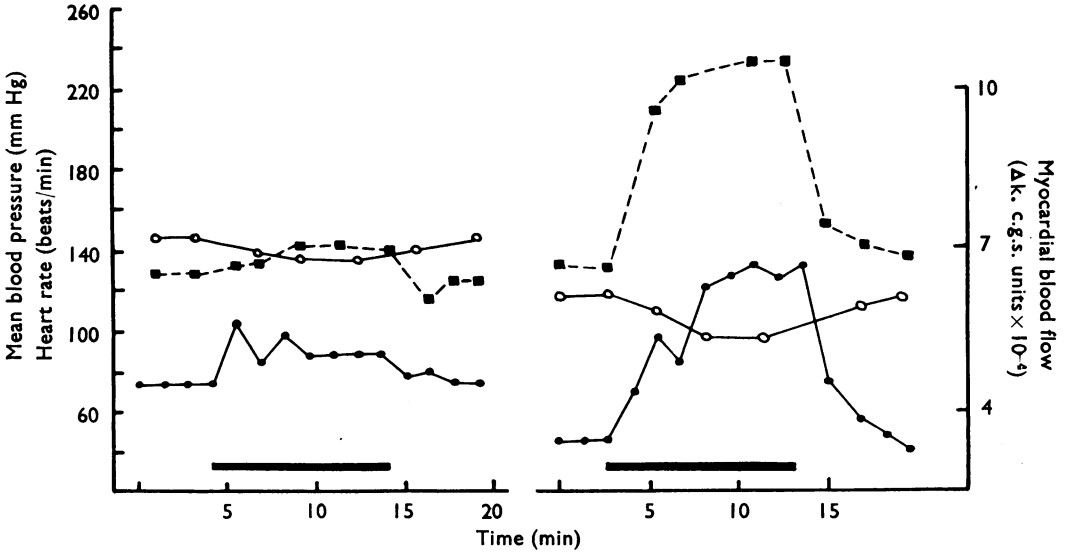

Fig. 3. The effect of intravenous infusions of adrenaline (0.25 μg/kg/min) on arterial blood pressure (■ - - - ■), heart rate (○——○), and left myocardial blood flow (●——●), before (on the left) and 3 hr after bretylium tosylate (10 mg/kg).

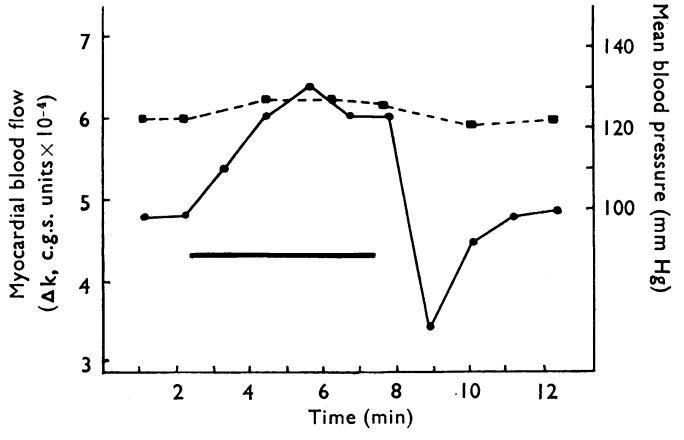

Fig. 4. Effect of stimulating the peripheral end of the left vagus nerve of an atropinized dog on arterial blood pressure (■ - - - ■) and left myocardial blood flow (●——●). These effects were abolished after adrenergic neurone blockade with bretylium tosylate (10 mg/kg).

"corrected temperature" (+0.24 and +0.32° C) and much smaller increases in heart rate (20 and 8 beats/min). In this dog bethanidine sulphate (3 mg/kg) reduced only the effects of nerve stimulation; after the drug left vagal nerve stimulation still increased flow by a mean of 62%, mean blood pressure by 75 mm Hg and heart rate by 10 beats/min. The changes in "corrected temperature" were however abolished.

DISCUSSION

The initial (sympathomimetic) effects of bretylium on heart rate and systemic blood pressure were similar to those described by Ledsome & Linden (1964), except that, in the present experiments, they were less marked. Thus Ledsome & Linden (1964) reported that, after bretylium, the mean arterial blood pressure increased by about 100 mm Hg (from an initial level of 131 mm Hg) and the heart rate by 150 beats/min (from an initial rate of 97 beats/min). The corresponding increases in the experiments reported here were 30 mm Hg and 15 beats/min from initial levels of 139 mm Hg and 164 beats/min. These differences are probably related to depth of anaesthesia (Ledsome & Linden's dogs were lightly anaesthetized) and to the anaesthetic agent used. The initial effects of bretylium on arterial blood pressure, heart rate, and myocardial blood flow and vascular resistance are almost certainly due to the release of catecholamines from adrenergic tissues since these same effects are also seen when the sympathetic nerves to the heart are stimulated (Denison & Green, 1958; Granata, Olsson, Huvos & Gregg, 1965) or when adrenaline is injected intravenously (Parratt, 1965). A local release of catecholamines from the myocardium into coronary venous blood following bretylium administration has, in fact, been clearly demonstrated by Gilmore & Siegel (1962) in a canine right heart bypass preparation.

The sympathomimetic effects were transient, and 30–90 min after the injection it can be assumed that the sympathetic post-ganglionic fibres to the heart are blocked (Ledsome & Linden, 1964). During this period left myocardial blood flow was 14–28% below normal and myocardial vascular resistance was increased by about 20%. This increase in the resistance of the myocardial vessels could theoreticaly be related to decreased cardiac work, which presumably follows sympathetic nerve block, or to decreased myocardial vasodilator tone. Taken in conjunction with the results of experiments in which β-adrenergic receptors were blocked with propranolol (Parratt & Grayson, 1966), it can probably be concluded that the myocardial vessels are under continuous sympathetic vasodilator tone. Thus after propranolol the increase in myocardial vascular resistance was of the order of 42%, whereas after bretylium the increase was 20%. The difference can be explained if one supposes a continual release of adrenaline/noradrenaline, from the sympathetic nerve endings around the vessels, predominantly influencing β-adrenergic receptors. If this release is prevented by bretylium, vasodilator tone is abolished and hence resistance to flow increases. On the other hand, if the release is not prevented but the β-receptors are blocked, there is a still greater increase in resistance due to activation of myocardial vascular α-receptors by the released catecholamines. There is considerable evidence that both types of receptor are present within the myocardial vasculature (see Parratt, 1967). If changes in myocardial vascular resistance following adrenergic receptor or neurone blockade were due entirely to changes in myocardial metabolism, one would not expect there to be any marked difference in resistance following these two procedures. It seems clear, therefore, that an adrenergic transmitter is being continuously released from nerve endings around the walls of the myocardial vessels.

After bretylium the effects of intravenous infusions of adrenaline on arterial blood pressure and on myocardial blood flow were potentiated by from 2 to 5 times. This

increased effect on myocardial blood flow was much greater than one would expect from the exaggerated pressor response, and one can therefore conclude that there is a potentiation by bretylium, not only of the vasoconstrictor effects of adrenaline, but also of the vasodilator effects on the myocardial vessels. It is doubtful whether bretylium has any selective effect on the receptor site itself, since both α and β actions of adrenaline are potentiated to the same extent. This is in marked contrast to the effects of adrenaline after β-receptor blockade where, although the pressor effect is exaggerated, the vasodilator effect on the myocardial vessels is actually reversed (Parratt, 1965). It is also clear from these results that bretylium has no effect, at this dosage level, on parasympathetic cholinergic transmission in the vagus nerve, since there was bradycardia during the adrenaline hypertensive response (Table 3) which was abolished by bilateral vagotomy. This supports the conclusion of Ledsome & Linden (1964) that bretylium, in a dose of 10 mg/kg, can be used to produce specific blockade of sympathetic nerves to the canine heart and indicates that bretylium is a useful tool in the study of problems concerned with coronary reflexes involving sympathetic nerves, such as those following experimental coronary occlusion (Grayson & Lapin, 1966 ; Grayson, Irvine, Parratt & Cunningham, 1967). An observation which might also be mentioned is that the effect of adrenaline on the myocardial vessels, both before and after bretylium, appears to be reduced by vagotomy. This reduction occurs despite the fact that the effects of adrenaline on blood pressure and heart rate are increased after vagotomy. These findings can be interpreted as indicating that, during increased reflex vagal activity (such as at the height of the adrenaline induced pressor response), released acetylcholine directly affects the coronary vessels (inducing vasodilatation) as well as the pacemaker. There is in fact considerable evidence that acetylcholine dilates the coronary vessels by an effect quite apart from those on the pacemaker or on extravascular support (see for example, Denison & Green, 1958).

In their original paper on the pharmacology of bethanidine, Boura & Green (1963) stated that in dogs (anaesthetized with sodium pentobarbitone) it raised the arterial pressure by between 70 and 110 mm Hg and this effect lasted for 10 to 30 min. Using a comparable dose (3 mg/kg), a less pronounced pressor effect was observed in the experiments described, although the effect was considerably more prolonged. The sympathomimetic effects of bethanidine on heart rate and on myocardial flow were equally pronounced and prolonged and this made it more difficult to use these experimental animals for a study of coronary reflexes.

The " reversed action " of acetylcholine, and of vagal stimulation, on the heart (see Dale, Laidlaw & Symons, 1910 ; Middleton, Middleton & Toha, 1949) is due to the release of myocardial noradrenaline (Richardson & Woods, 1959). On the basis of experiments in which noradrenaline administration failed to restore the sympathomimetic effect of acetylcholine in isolated sympathectomized hearts but did restore it in reserpinized hearts, Cabrera, Cohen, Middleton, Utano & Viveros (1966) came to the conclusion that the source of this noradrenaline was post-ganglionic sympathetic fibres and not an extra-neuronal site. The experiments described here support this conclusion, since in almost all the experiments adrenergic neurone blockade prevented the sympathomimetic effects of released acetylcholine in atropinized dogs.

SUMMARY

1. The effects of bretylium and of bethanidine on blood pressure, heart rate, left myocardial blood flow (measured by a heated thermocouple method) and myocardial metabolic heat production, were studied in anaesthetized dogs.

2. Bretylium initially raised arterial blood pressure and increased heart rate and myocardial flow, indicating a decrease in myocardial vascular resistance. When adrenergic neurone blockade was complete, myocardial metabolic heat production was raised and arterial pressure, heart rate and myocardial flow was reduced. Evidence is adduced which suggests that, under normal conditions, an adrenergic transmitter is being continuously released from nerve endings around the walls of the myocardial vessels, which induces vasodilatation.

3. Bethanidine raised arterial blood pressure and increased heart rate and myocardial flow. These effects were still apparent 1–2 hr after the injection.

4. The effects of intravenous infusions of adrenaline on arterial blood pressure and on myocardial flow were potentiated 2–5 times in bretylium treated dogs.

5. Stimulation of the peripheral end of the cut vagus nerves in atropinized dogs resulted in an increase in blood flow through the left myocardium. This was abolished or markedly reduced after bretylium.

6. It is suggested that bretylium is a useful agent for the study of coronary reflexes involving sympathetic fibres.

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