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THE EFFECTS OF BRETYLIUM AND GUANETHIDINE ON THE PRESSOR RESPONSES TO NORADRENALINE AND ANGIOTENSIN

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In normal human subjects the intravenous administration of bretylium and guanethidine rapidly increased the pressor response to intravenous infusions of noradrenaline, while the response to angiotensin was little or not affected. This result suggests that potentiation of noradrenaline by bretylium and guanethidine is not simply due to block of homeostatic reflexes, but is due to sensitization of arteriolar smooth muscle. But we, like others, have failed to demonstrate such an effect in man when measuring changes in blood flow during intra-arterial infusions of noradrenaline.

This paper describes some experiments on the interaction between noradrenaline and the hypotensive drugs, bretylium and guanethidine, on the blood pressure of man. Bretylium sometimes increases blood pressure when it is given to patients with hypertension caused by a phaeochromocytoma (Laurence & Rosenheim, 1960) and this observation was the starting point for these investigations.

We have confirmed in man the findings in animals that the administration of these hypotensive drugs is followed by an enhancement of the pressor effect of intravenous infusions or injections of noradrenaline (Boura & Green, 1959 ; Maxwell, Plummer, Schneider, Povalski & Daniel, 1960). We have also attempted to test two hypotheses concerning the mechanism of the potentiation of noradrenaline. The first postulates that there is increased sensitivity of the effector tissue to noradrenaline ; the second that the greater increase in blood pressure is due to block of cardiovascular reflexes which normally modify and reduce the pressor effect of noradrenaline (Doyle, Fraser & Marshall, 1959 ; Hodge & Whelan 1962).

We conclude that, while the first of these hypotheses is supported by the greater weight of evidence, there remain certain of our observations which are better explained by the second. A small portion of these results has already been briefly reported (Laurence & Nagle, 1961).

METHODS

Experimental subjects

The majority of experiments were performed on normal volunteers who were colleagues or students. Some experiments were performed on volunteer patients with hypertension who were receiving, or about to receive, bretylium as continuous treatment. The patients all had moderately severe hypertension with diastolic blood pressures over 115 mm Hg but with no evidence of the complications of a raised blood pressure.

Drugs

Except for the treated hypertensive patients, who were receiving bretylium by mouth in doses of 900 to 1,800 mg/day, all drugs were injected intravenously. Bretylium was given in doses of 100 to 400 mg as a 5% solution; in most experiments 200 mg were given. In every case the dose was sufficient to cause diastolic hypotension when the patient or subject was tilted to the erect position or changes in the vascular responses to Valsalva's manœuvre characteristic of sympathetic block. Guanethidine, in doses of 20 mg, was given as a 0.04% solution because more concentrated solutions caused local pain.

Noradrenaline (Levophed, Bayer) and angiotensin (Hypertensin, Ciba) were dissolved at suitable concentration in 5% dextrose solution and were infused from power-driven 50 ml. syringes whose rate of delivery could be continuously varied. Therefore, when it was desired to give noradrenaline and angiotensin in equipressor doses, the response to a given dose of noradrenaline could be matched by altering the rate of infusion of angiotensin until a similar rise in blood pressure was obtained. Intravenous infusions were given for a period of 10 min and intra-arterial infusions for 3 to 5 min.

Measurement of blood pressure and blood flow

In many experiments, especially those of long duration, the blood pressure was measured with a sphygmomanometer. In others it was measured through a needle inserted into the left brachial artery and connected to a pressure transducer. The pressor effect of noradrenaline was measured with the subjects supine. Mean pressure was calculated from the formula:

$$\text{mean pressure} = (\text{systolic pressure} + \text{twice diastolic pressure})/3$$

Forearm blood flow was measured by a mercury-in-rubber plethysmograph (Whitney, 1953) placed over the forearm at its point of maximum diameter. When intra-arterial infusions were given the blood pressure was also measured through the same needle, the rate of flow being small enough not to interfere with pressure measurement.

A sphygmomanometer cuff around the wrist was inflated to 200 mm Hg in order to occlude the circulation to the hand during measurements of blood flow.

RESULTS

The effect of bretylium alone on the blood pressure of supine subjects

Table 1 shows that bretylium had little effect on the blood pressure of the supine normal subjects when they were not receiving infusions of noradrenaline. The

TABLE 1

BLOOD PRESSURES (MM/HG) OF FOURTEEN SUPINE NORMAL SUBJECTS BEFORE AND AFTER BRETYLIUM

Before bretylium			After bretylium			Change in mean pressure
Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	
134	71	92	137	71	92	0
120	75	90	130	80	97	+7
115	80	92	120	80	93	+1
128	80	96	130	65	87	−9
124	72	84	125	75	92	+8
127	90	102	137	90	106	+4
112	70	84	118	70	86	+2
112	70	84	120	70	87	+3
106	68	81	110	70	83	+2
132	70	91	145	75	98	+7
106	86	79	112	66	81	+2
116	75	89	116	75	89	0
108	67	81	120	75	90	+9
98	60	73	98	58	72	−1
						Average +2·5

commonest response was a small increase in mean pressure which averaged 2.5 mm Hg for the group. This increase was considerably less than the change with noradrenaline, either before or after bretylium.

The effects of bretylium and intravenous noradrenaline

Fig. 1 shows the effect of intravenous infusions of noradrenaline on the blood pressure of four normal subjects before and after they had received bretylium. Potentiation by bretylium of the pressor effect of noradrenaline was also found in

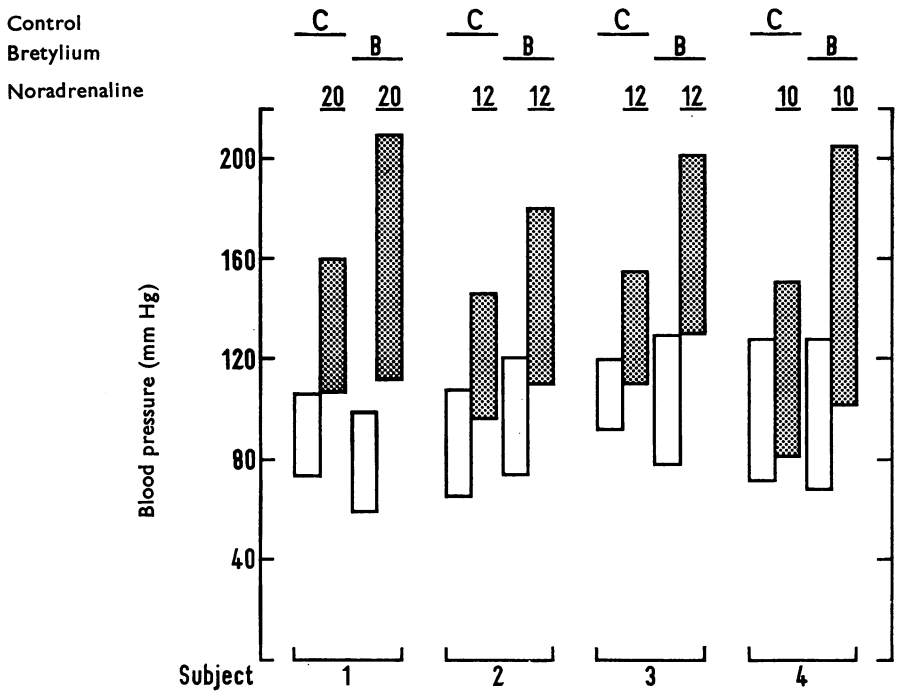

Fig. 1. Modified from Laurence & Nagle (1961). Blood pressures, resting (empty columns) and during (filled columns) intravenous infusions of noradrenaline (doses in μg/min at top) given to four subjects before (left-hand pairs of columns, C) and after (right-hand pairs of columns, B) bretylium.

a further four normal subjects and in three hypertensive patients who were given noradrenaline both while they were not being treated and also while they were on continuous treatment with bretylium (oral dose, 900 to 1,800 mg/day). Because hypertensive patients are more sensitive than normal subjects to the pressor action of noradrenaline (Doyle *et al.*, 1959) and because we did not wish to increase their blood pressure by more than a modest amount, the dose of noradrenaline used (4 μg/min) was smaller than that given to the normal subjects (8 to 20 μg/min).

Table 2 shows how the pulse rate was slowed during an infusion of noradrenaline whether bretylium had been given or not.

TABLE 2
PULSE RATES (PER MIN) BEFORE AND DURING INTRAVENOUS INFUSIONS OF NORADRENALINE BEFORE AND AFTER BRETYLIUM

Before bretylium			After bretylium		
Before noradrenaline	During noradrenaline	Change	Before noradrenaline	During noradrenaline	Change
72	54	−18	72	51	−21
64	48	−16	60	48	−12
58	46	−12	58	46	−12
73	55	−18	73	58	−15
70	58	−12	72	58	−14
68	56	−12	72	56	−16

Further experiments were performed to determine how soon potentiation developed after the administration of bretylium and how long it persisted. Fig. 2 shows portions of a continuous record of the blood pressure of a normal subject who was given 100 mg of bretylium intravenously whilst receiving an intravenous infusion of noradrenaline. There was a transient fall in blood pressure during the actual injection of bretylium, but within 7 min the blood pressure had risen to a new, higher, level. On stopping the noradrenaline infusion, the blood pressure fell to its original control value. This almost immediate effect of bretylium in potentiating

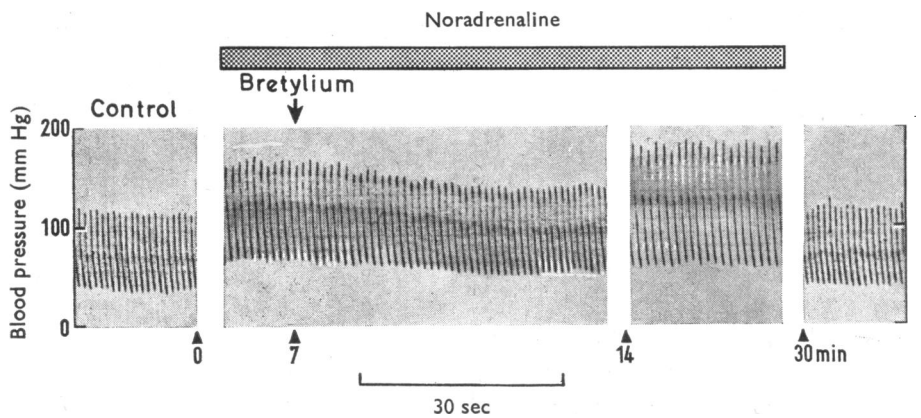

Fig. 2. Parts of a continuous record of the blood pressure of a normal subject who was given bretylium (100 mg, intravenously at arrow) during an intravenus infusion of noradrenaline (4 μg/min during bar). Times (min) are given from the start of the noradrenaline infusion.

noradrenaline was confirmed in other experiments and in particular in the one illustrated in Fig. 3, in which noradrenaline infusions were given every 30 min to a subject before and after receiving first a control injection of saline and then an injection of 200 mg of bretylium. A maximum pressor effect was obtained immediately after the bretylium had been given and the response then declined slowly over the next 3 hr.

We also investigated how different doses of bretylium affected the degree of potentiation. Knowing that maximal potentiation of noradrenaline is almost immediate after a single dose of bretylium, we gave 50 mg of bretylium every 30 min

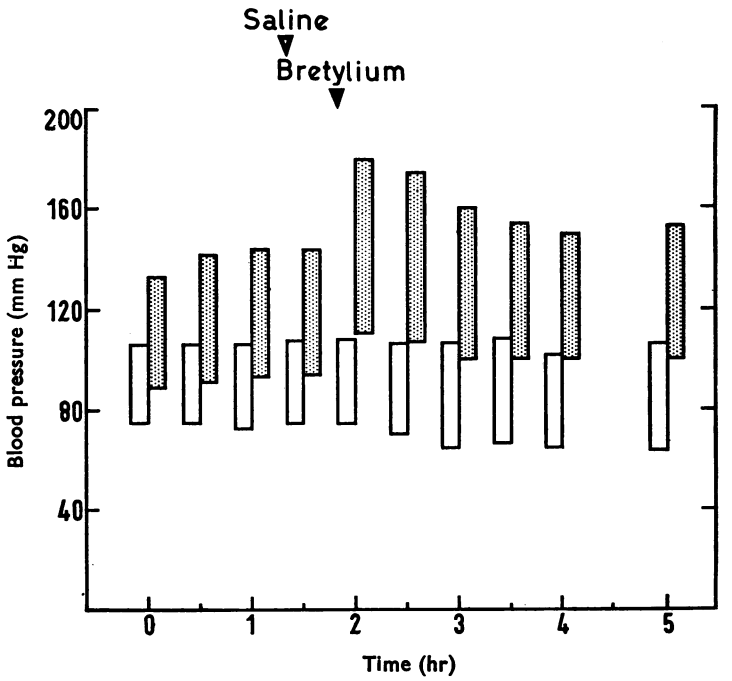

Fig. 3. Blood pressure, resting (empty columns) and during (filled columns) intravenous infusions of noradrenaline (8μg/min) before, and at various times after, the intravenous administration of a saline control (at first arrow) and bretylium (200 mg, at second arrow).

to two normal subjects, each dose being followed by an infusion of noradrenaline. Fig. 4 shows that the pressor effect increased with increasing doses of bretylium up to total doses of 350 and 400 mg.

The effect of bretylium and intravenous angiotensin

The effect of bretylium on the pressor action of angiotensin was studied in order to help elucidate the mechanism of potentiation of noradrenaline. Angiotensin was given in intravenous infusions of 2 μg/min to four normal subjects before and after they had received bretylium. Their responses (Fig. 5) show that the pressor effect of angiotensin was very much less affected by bretylium than was that of noradrenaline (Fig. 1). This result was confirmed in two subsequent experiments in which equipressor doses of angiotensin and noradrenaline were given to normal subjects before and after bretylium (Fig. 6).

The effect of bretylium and intra-arterial noradrenaline

Forearm blood flow was measured during intra-arterial infusions of, first, 0.9% saline, and then noradrenaline. After 20 min from the intravenous administration of 150 to 200 mg of bretylium these measurements were repeated and, finally at the end of the experiment, an intravenous infusion of 10 μg/min of noradrenaline was given in order to confirm that the dose of bretylium had been sufficient to

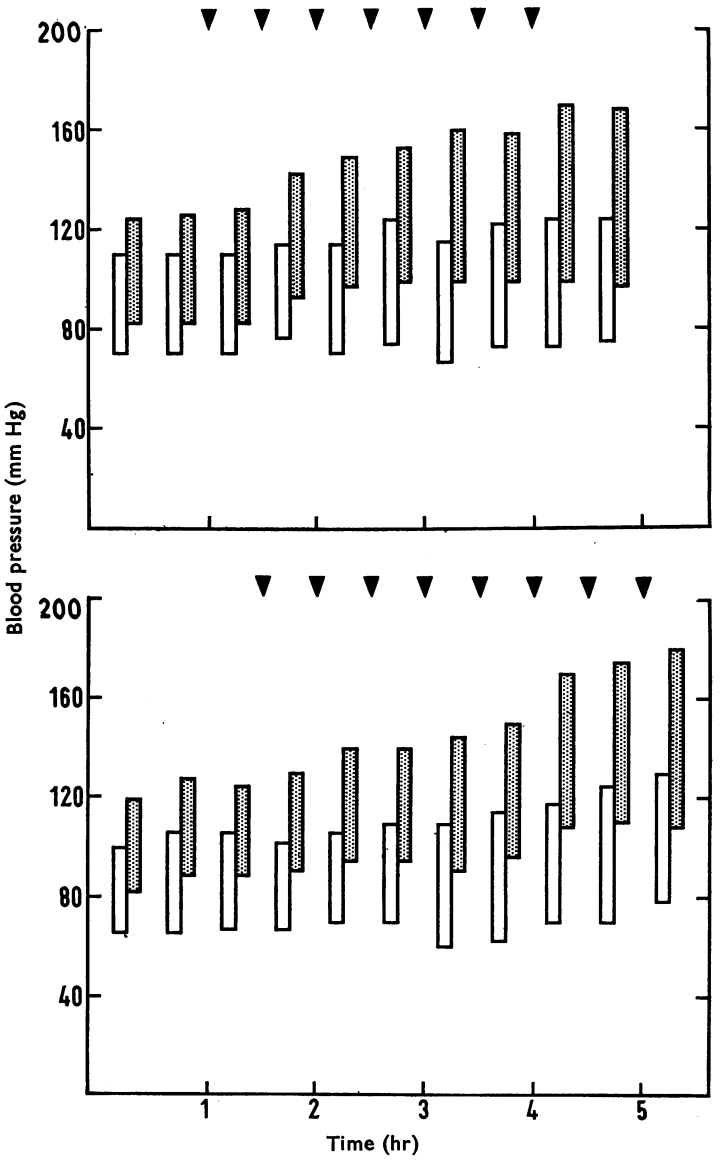

Fig. 4. Blood pressure, resting (empty columns) and during (filled columns) intravenous infusions of noradrenaline (8 μg/min) given after repeated small doses of bretylium (50 mg/30 min, at arrows) to two subjects.

potentiate the pressor effect of intravenous noradrenaline. Resting blood flows were little affected by the doses of bretylium used.

The results are shown in Table 3. The percentage fall in forearm blood flow during an intra-arterial infusion of noradrenaline was not significantly altered by bretylium.

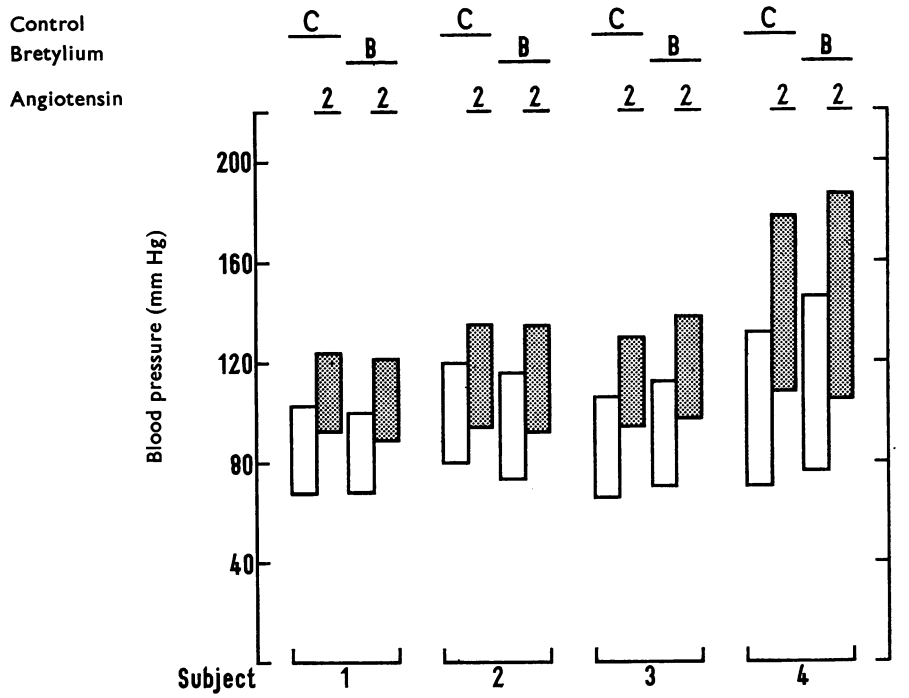

Fig. 5. Blood pressures, resting (empty columns) and during (filled columns) intravenous infusions of angiotensin (2 μg/min), given to four subjects before (left-hand pairs of columns, C) and after (right-hand pairs of columns, B) bretylium.

The effect of guanethidine and intravenous noradrenaline and angiotensin

Fig. 7 shows the effects of equipressor doses of noradrenaline (8 μg/min) and angiotensin (1.6 μg/min) before and after the injection of two successive doses of 20 mg of guanethidine. As with bretylium, the pressor effect of noradrenaline was enhanced by guanethidine and more so with the bigger dose of guanethidine. The effect of angiotensin was substantially unchanged by guanethidine.

TABLE 3

FOREARM BLOOD FLOW DURING INTRA-ARTERIAL INFUSIONS OF NORADRENALINE BEFORE AND AFTER BRETYLIUM

	Forearm blood flow (ml./100 ml. of tissue)					
	Before bretylium			After bretylium		
Intra-arterial noradrenaline (μg/min)	Resting	During noradrenaline	% change	Resting	During noradrenaline	% change
0·2	4·2	1·9	−54·7	3·6	1·6	−55·5
0·2	3·8	2·0	−47·4	4·0	2·0	−50·0
0·2	4·3	2·0	−53·5	3·8	1·7	−55·5
0·2	4·5	2·1	−54·1	4·2	2·0	−52·3
0·1	4·2	2·2	−47·6	3·8	2·0	−47·4
0·1	3·8	2·2	−42·0	4·0	2·2	−45·0
0·05	4·2	2·5	−40·5	3·8	2·3	−40·6
0·05	4·0	3·0	−25·0	4·0	2·9	−27·5

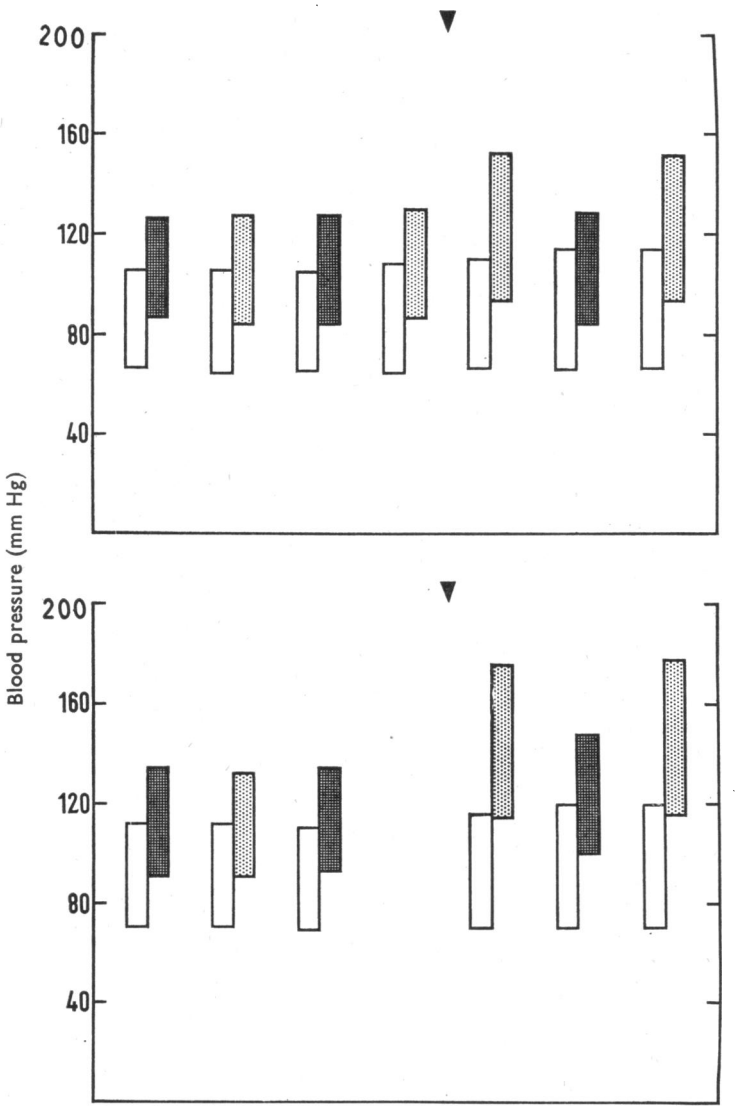

Fig. 6. Blood pressure, resting (empty columns) and during intravenous infusions of noradrenaline (10 μg/min, grey columns) or angiotensin (2 μg/min, dark columns) given to two subjects before and after bretylium (200 mg, intravenously at arrows). Duration of infusions, 10 min; interval between infusions, 30 min.

DISCUSSION

The increase in blood pressure produced by an intravenous infusion of noradrenaline is principally due to a rise in peripheral resistance, the cardiac output (minute volume) remaining nearly constant in normal subjects. There is some evidence that in man noradrenaline would increase cardiac output were this not countered by reflex vagal bradycardia so that although the stroke volume increases

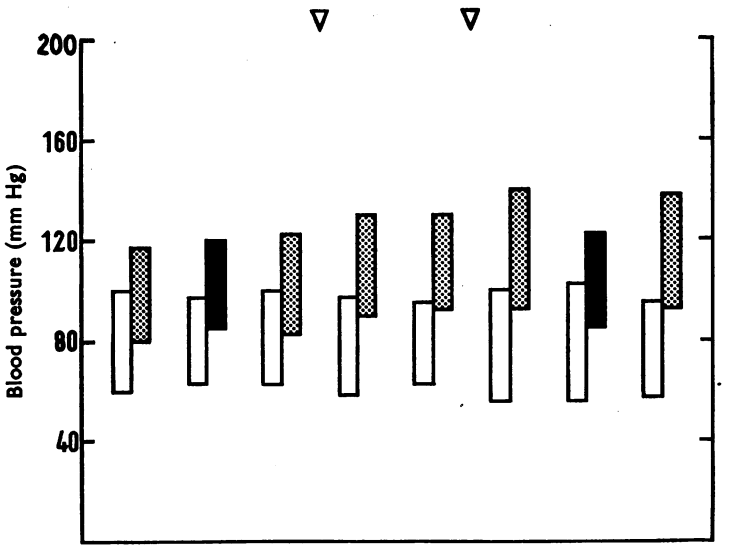

Fig. 7. Blood pressures, resting (empty columns) and during intravenous infusions of noradrenaline (8 μg/min, grey columns) and angiotensin (1·6 μg/min, dark columns) given before and after guanethidine (20 mg, intravenously at arrows). Duration of infusions, 10 min; interval between infusions, 30 min.

the minute volume does not (Goldberg, Bloodwell, Braunwald & Morrow, 1960). A drug, such as atropine, which blocks the reflex bradycardia might therefore be expected to increase the pressor response to noradrenaline and was, in fact, found to do so by Geffen & Ross (1956). Bretylium and guanethidine, on the other hand, have no effect on the parasympathetic system when given in therapeutic doses and, as shown in Table 2, did not affect the bradycardia during noradrenaline infusions. It is clear that modification of reflex vagal bradycardia does not contribute to this potentiation of noradrenaline.

We therefore directed our attention to the action of noradrenaline on peripheral resistance and considered two hypotheses: one, that potentiation is due to an increase in sensitivity to noradrenaline of the effector tissue; the other, that the increased pressor effect is due to block of reflexes, with non-vagal efferent paths, which usually modify and reduce the pressor effect of noradrenaline.

Perhaps the strongest evidence in favour of the first of these hypotheses is that potentiation is readily observed in organs, such as the nictitating membrane, which are not known to possess any reflex mechanism, such as the cardiovascular system does, for buffering the effects of noradrenaline. However, it might be unwise to dismiss the hypothesis of potentiation by reflex block on these grounds alone, for the fact that the adrenergic effector tissue is supersensitive to noradrenaline in animals does not rule out the possibility that reflex block might be quantitatively more important in man. We therefore investigated the interaction between the hypotensive drugs and angiotensin, arguing that if potentiation of the effects of noradrenaline were due to block of reflexes elicited by a rise in blood pressure, then the pressor effect of an intravenous infusion of angiotensin should be similarly

enhanced, while, on the other hand, an increase in the sensitivity of the effector tissue for noradrenaline might well leave the response to angiotensin unaffected. We found (Figs. 6 and 7) that the pressor action of angiotensin was much less affected by bretylium and guanethidine than was that of noradrenaline and we consider these results to be evidence against reflex block as an important cause of potentiation of noradrenaline, though such a block could explain the much smaller degree of potentiation sometimes seen with angiotensin.

Our experiments with intra-arterial infusions of noradrenaline were designed to test the two hypotheses from a different standpoint. The use of intra-arterial infusions enabled us to measure the local vasoconstrictor effect of noradrenaline while the small doses did not affect the blood pressure and were therefore unlikely to elicit any reflex response. By giving the bretylium intravenously we were able to satisfy ourselves that potentiation of the pressor effect of intravenous infusions of noradrenaline had occurred whatever the response to the intra-arterial infusions might be. Potentiation of the pressor effect of intravenous noradrenaline did occur after bretylium in every instance. By contrast the effect of intra-arterial noradrenaline on blood flow was unaltered after bretylium. These results are in accord with those of Blair, Glover, Kidd & Roddie (1960), who gave noradrenaline (1.0 μg/min) intra-arterially, and of French & Matthews (1961), who gave 20 μg/min intravenously. Neither group of workers found any alteration in the fall of blood flow induced by noradrenaline after bretylium, but both gave the bretylium intra-arterially and in this respect their experiments differed from ours.

We find therefore that, while bretylium always enhanced the pressor effect of *intravenous* infusions of noradrenaline, the vasoconstrictor effect of *intra-arterial* infusions into the forearm was unaffected.

These results seem to suggest that potentiation of the pressor response is due not to increased sensitivity of effector tissues but to block of homeostatic reflexes which are only active when the blood pressure is raised by an intravenous infusion of noradrenaline. They are, however, in conflict with the conclusions we draw from our experiments with angiotensin and we may speculate as to why this is so.

It may be that the doses of noradrenaline given intra-arterially were too big. They were certainly relatively bigger than the doses given intravenously. We were unable to investigate the effect of smaller doses for technical reasons, but the possibility remains that smaller, and more physiological, intra-arterial doses of noradrenaline might produce a fall in forearm flow which became greater after bretylium. A further possibility is that the greater pressor response to intravenous infusions of noradrenaline is due to an enhanced direct effect on the myocardium and such a mechanism would be compatible with all our findings without invoking sensitization of peripheral vessels.

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