RESULTS

Effects on heart rate and blood pressure of repeated doses of angiotensin at about 20 min. intervals

The effects of angiotensin were observed upon four intact dogs under morphine and chloralose. In some of them doses were repeated. When the heart rate and respiration became constant after chloralose the angiotensin was injected.

As shown in Table I and fig. 1, the heart rate began to decrease shortly after giving the injection. The most marked effect in the majority of cases was around 30 sec. after giving the drug. The maximum slowing in most cases with 10 µg dose of angiotensin was around 15 - 20 beats. Once the blood pressure reached a peak and stayed there for awhile, the heart rate immediately started rising, and in most cases it returned to the basal level within about 1½ min. to 2 min. after giving the injection of angiotensin. Then it continued rising above the basal level about 15 - 20 beats. Reaching this height, it started declining again. The rise of blood pressure was found somewhat proportional to the dose.

The results show that 1) angiotensin brings about slowing of heart rate when given in these doses, 2) the

TABLE 1

EFFECTS ON HEART RATE OF REPEATING DOSES OF ANGIOTENSIN AT ABOUT 20-MINUTE INTERVALS

Dog No.	Dosage of angiotensin in µg.	Heart rate in beats per minute at 10-second intervals after beginning of injections																			Initial decrease in heart rate in beats/min.	Later increase in heart rate in beats/min.
		-20	-10	10	20	30	40	50	1:00	10	20	30	40	50	2:00	3:10	4:10	9:10	12:10	15:10		
6	2.5	60	63	63	63	57	57	54	51	57	57	57	54	54	60	63	66	69			12	6
6	5	60	57	57	60	48	42	42	57	60	60	60	60	57	57	69	69				18	9
6	10	57	60	51	48	42	42	48	60	66	63	60	63	63	63	63	66				18	9
6	20	57	57	63	42	39	48	66	66	78	78	78	54	66	84	66	69	66			18	21
6	5	66	66	66	60	48	48	45	57	66	63	57	66	73	78	66	66				18	12
7	10	81	81	78	63	63	84	81	78	87	93	99	87	90	87	93	93	78	78	81	18	18
7	10	75	78	78	63	66	87	80	78	87	93	81	81	96	93	96	93	93	84	81	15	21
7	20	75	69	66	69	69	78	87	57	57	102	96	72	66	69	99	99	93	93	84	18	24
10	10	85	87	85	72	60	65	65	66	72	69	78	72	81	87	96	105	99	102	105	27	18
10	10	85	83	87	66	66	66	63	66	66	69	69	72	75	84	96	96	102	96	93	22	17
12	10	78	78	78	72	67	66	63	60	66	66	78	78	78	78	96	108	108	108	108	18	30

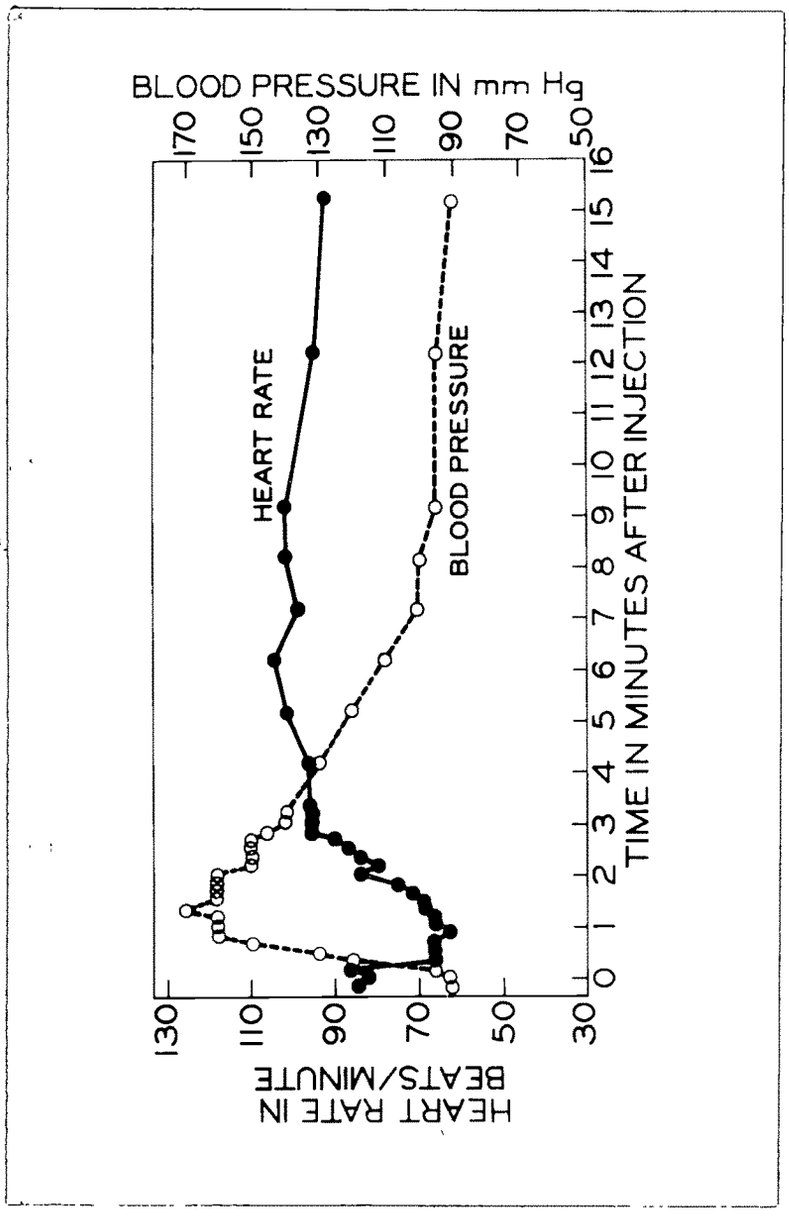

Fig. 1: Effect of angiotensin (10 µg.) on heart rate and blood pressure under the influence of morphine and chloralose (same anaesthetic agent used throughout).

slowing seems to be related to the quick rise of blood pressure, 3) tachyphylaxis was not observed.

Effects of Pitressin on heart rate and blood pressure of dogs when given in repeated doses at about 20 min. intervals

To compare the effect of angiotensin on heart rate with another vasopressor drug, Pitressin was injected (0.1 unit/kg) intravenously in six intact dogs under chloralose anaesthesia. It was noted that heart rate started slowing shortly after giving the injection (fig. 2b) and the greatest effect was around 30 sec. after giving the drug. In the majority of cases the maximum slowing was near 30 - 50 beats (Table 2). The heart rate had not returned to basal level 15 min. after giving the injection. The blood pressure rose quickly and then came down. The heart rate did not come back to the basal level, even when blood pressure started declining. The lower dosage of Pitressin (0.05 unit/kg) did not make a difference in type of action of the drug, while higher doses (0.2 unit/kg) caused cardiac irregularities (dogs 6 and 7). Tachyphylaxis was not observed in any dog in these experiments.

The results indicate 1) the cardioinhibitory action of Pitressin is marked, 2) the slowing continues for

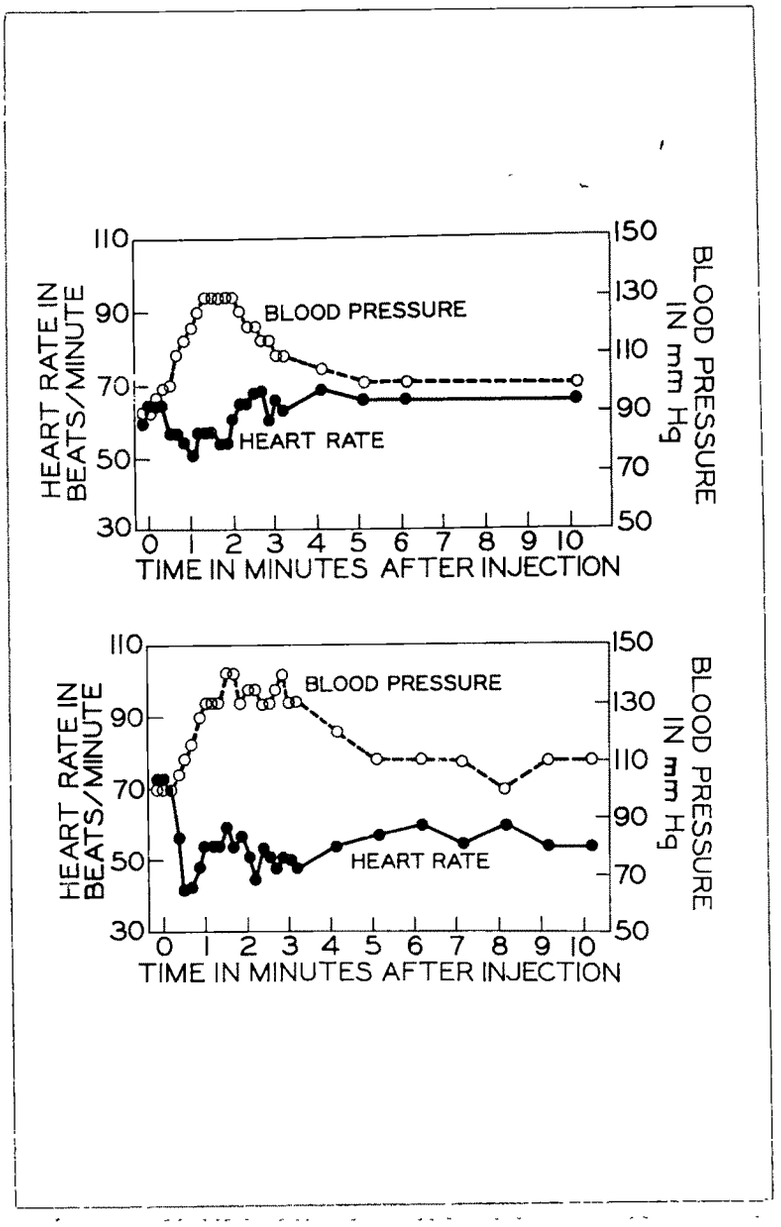

Fig.2 : Comparison of cardioinhibitory responses to equipressor doses of angiotensin and vasopressin in the same dog.

Above - angiotensin
Below - Vasopressin

EFFECTS ON HEART RATE OF REPEATING DOSES OF PITRESSIN AT ABOUT 20-MINUTE INTERVALS

Dog No.	Dosage of Pitressin in units	Heart rate in beats per minute at 10-second intervals after beginning of injections																		Decrease in heart rate in beats/minute
		-20	-10	10	20	30	40	50	1:00	10	20	30	40	50	2:00	3:10	4:10	9:10	12:10	15:10	
1	1.10	84	84	84	54	48	42	42	42	42	42	42	42	42	42	38	38	48			46
1	1.10	72	72	72	60	48	50	48	48	48	48	48	48	48	48	48	50	58	60	72	24
1	1.10	60	60	58	50	48	48	48	48	48	48	48	48	48	48	44	46	46	52	56	16
3	1.25	102	102	87	42	42	36	36	36	36	36	36	36	36	36	38	45	48			66
3	1.25	66	66	54	33	33	33	33	33	35	39	39	39	39	39	39	45	57			33
4	0.65	78	76	72	66	66	66	63	54	54	48	48	48	48	48	48	50	60	63	64	30
4	0.65	66	66	66	57	56	56	56	54	50	48	42	42	42	42	42	44	54	56	56	24
4	0.65	66	63	60	57	50	50	50	50	48	44	42	42	42	42	44	46	54	54	54	24
5	1	114	114	102	70	63	54	57	63	66	66	66	66	66	66	66	66	72	78	96	60
5	1	104	104	102	66	45	48	48	54	54	57	57	57	57	57	66	66	72	80	88	59
5	1	102	102	102	60	54	60	60	60	60	60	60	60	60	60	60	66	72	75	80	48
6	2	84	84	84	60	39	54	60	66	66	66	66	66	57	51	54	54	66	66	66	45
6	2	72	72	70	57	42	42	48	54	54	54	60	54	57	51	48	54	54	54	63	30
6	4	60	60	60	45	30	30	40	72	78	65	78	81	66	51	48	48	48	48	55	30
7	2	78	78	78	60	42	44	48	48	54	54	51	48	48	51	48	51	69	69	78	36
7	4	72	72	69	57	42	45	51	54	54	57	60	57	60	60	54	54	58	60	60	30

a long time, even when blood pressure starts declining, 3) tachyphylaxis was not observed.

Comparison of cardioinhibitory responses to equipressor and other doses of angiotensin and Pitressin in the same dog

Since the two compounds exhibited different types of action on heart rate the effects of equipressor doses in the same dog were compared.

Experiments were performed on the same dogs using Pitressin on one day and angiotensin on the other. Different doses were used to pick up the equipressor effects of two drugs for comparison. Two dogs were used for this purpose.

The general pattern of action of the two drugs was the same as observed in the previous results. The equipressor effects were obtained with 2 units Pitressin and 2.5 µg angiotensin (Table 3, dog 6) and also with 4 units Pitressin and 10 µg angiotensin (Table 3, dog 7). When the results are compared (figs.2a and 2b), it is seen that the maximum slowing caused by Pitressin was 30 beats, while with an equipressor dose of angiotensin it was 9 beats. The heart rate in the case of Pitressin did not return to normal upto the end of the experiment

TABLE 3

EFFECTS ON HEART RATE OF EQUIPRESSOR DOSES OF ANGIOTENSIN AND PITRESSIN

Dog No.	Drug and amount	Rise of blood pressure in mm. Hg.	Basal heart rate/ min. before injection	Minimum heart rate / min. after injection	Decrease in heart rate/min.	Time when heart rate is at basal level again after injection	Maximum heart rate / min. after injection	Increase in heart rate/min.
6	Angiotensin 2.5 µg.	40	60	51	9	2 min.	69	9
6	Pitressin 2 units	40	84	39	45	Beyond 15 min.	66	0
6	Pitressin 2 units	40	72	42	30	Beyond 15 min.	63	0
7	Angiotensin 10 µg.	70	81	63	18	30 sec.	99	18
7	Pitressin 4 units	60	72	42	30	Beyond 15 min.	60	0

while in the case of angiotensin it was at basal level at 2 min. after injection of the drug and then rose about 6 beats above the basal level.

From the comparison of equipressor doses of angiotensin and Pitressin it wasfound that 1) the tendency of angiotensin to produce slowing of the heart rate is less marked than for Pitressin, 2) in the case of angiotensin heart rate takes less time to come up to the basal level and then it rises above the basal level despite the elevated arterial pressure, 3) the slowing in the case of angiotensin is present only during the phase of quick rise of blood pressure.

Pitressin administration during buffering of blood pressure

The experiments were performed on two dogs in which the mechanical buffer system was used. The results were obtained when the arterial pressure was buffered and when it was not buffered (Table 4). It was seen that the rise of blood pressure was buffered to a great extent but not completely.

The heart rate slowed in both cases whether or not the blood pressure was buffered and did not return to basal level until the end of the experiment. The

TABLE 4

EFFECTS OF ANGIOTENSIN AND PITRESSIN ON HEART RATE DURING BUFFERING OF ARTERIAL BLOOD PRESSURE

Dog No.	Drug and amount	Tube to compensator	Rise in blood pressure in mm.Hg.	Heart rate in beats per minute at 10-second intervals after beginning of injections														
				-20	-10	10	20	30	40	50	1:00	10	20	30	40	50	2:00	3:10	4:10
3	Pitressin 1.25 units	open	5	174	174	172	168	138	132	144	150	148	146	140	136	134	138	140	134
3	Pitressin 1.25 units	closed	25	114	110	110	78	69	66	70	70	66	63	66	66	69	72	84	90
3	Pitressin 1.25 units	open	0	102	96	96	84	66	60	60	60	63	66	72	78	84	84	84	84
3	Pitressin 1.25 units	closed	15	105	105	105	96	81	78	62	52	75	75	75	78	78	81	84	93
3	Pitressin 1.25 units	open	5	132	132	132	132	108	105	108	108	110	114	117	120	120	123	135	141
8	Angiotensin 10 µg.	open	20	138	138	138	138	162	186	216	234	240	240	240	240	237	234	210	183
8	Angiotensin 10 µg.	closed	40	144	141	138	129	135	138	144	138	135	132	132	132	132	132	138	156
8	Pitressin 3 units	open	15	156	156	150	138	132	132	126	120	120	120	114	114	111	111	120	
9	Angiotensin 10 µg.	open	20	90	96	150	216	264	276	252	240	234	234	222	222	222	216	198	192
9	Angiotensin 10 µg.	closed	60	120	126	120	102	156	132	114	123	123	126	129	138	138	138	138	141
20	Angiotensin 10 µg.	open	15	114	114	114	120	180	210	228	249	252	246	240	234	228	228	198	182
20	Angiotensin 10 µg.	closed	60	132	132	132	102	129	126	102	114	111	111	114	120	123	135	144	144
20	Angiotensin 10 µg.	open	20	144	144	150	144	180	198	210	216	210	207	195	192	186	180	144	126

TABLE 5

COMPARISON OF EFFECTS OF ANGIOTENSIN AND PITRESSIN ON HEART RATE AS INFLUENCED BY BUFFERING OF BLOOD PRESSURE

Dog No.	Drug and amount	Tube to compensator	Rise in blood pressure in mm. Hg.	Basal heart rate/min.	Minimum heart rate/minute after injection	Decrease in heart rate/min.	Maximum heart rate/minute after injection	Increase in heart rate/min.
3	Pitressin 1.25 units	open	5	174	132	42	172	0
3	Pitressin 1.25 units	closed	25	112	63	49	110	0
3	Pitressin 1.25 units	open	0	99	60	39	96	0
3	Pitressin 1.25 units	closed	15	105	52	53	105	0
3	Pitressin 1.25 units	open	5	132	105	27	132	0
8	Angiotensin 10 µg.	open	20	138	138	0	240	102
8	Angiotensin 10 µg.	closed	40	142	129	13	156	14
8	Pitressin 3 units	open	15	156	111	45	150	0
9	Angiotensin 10 µg.	open	20	93	150	0	276	183
9	Angiotensin 10 µg.	closed	60	123	102	21	156	33
20	Angiotensin 10 µg.	open	15	114	114	0	252	138
20	Angiotensin 10 µg.	closed	60	132	102	30	144	12
20	Angiotensin 10 µg.	open	20	144	144	0	216	72

maximum slowing differed depending upon 1) whether or not the blood pressure was buffered, 2) the dose of drug. The slowing was more marked when the blood pressure was not buffered (Table 5, dog 3) than when it was buffered (Table 5, dog 3). It was around 50 in the first case and around 40 in the latter. With larger doses of Pitressin (3 units) the slowing was more than with smaller doses (45 beats) although the blood pressure was buffered at the same time.

Therefore it could be said that 1) buffering reduces the cardioinhibitory response to Pitressin, although the basic pattern of action remains the same, 2) the slowing is somewhat proportional to the rise of blood pressure which in its turn depends upon dose of drug whether or not the blood pressure is buffered.

Change in effect of angiotensin on heart rate produced by buffering the blood pressure and its comparison with Pitressin in the same dog

The pattern of action of the same dose of angiotensin was different when the buffer system was in use and when it was closed. When it was in use, the rise of blood pressure could not be completely checked; however the heart rate did not decrease (figs. 3 and 4).

It started rising after giving the angiotensin. The maximum rise was of the magnitude of about 100 to 200 beats/min. (Table 5, dog 8 and dog 9). It reached a peak, then slowly decreased toward the control level (figs. 3 and 4).

When the buffer system was closed, the rise of blood pressure was very marked. There was slowing of the heart rate of the magnitude of 10 - 20 beats/min. (fig.4)(Table 5, dogs 8 and 9). The general pattern of slowing and increase was similar to that observed in intact dogs.

In the case of Pitressin (Table 5, dog 8) with the buffer system in use, the results were different, as already mentioned. When they are compared (fig.3) with angiotensin the difference is as follows:
1) Buffering changes the pattern of action of angiotensin (fig.4). No initial slowing of heart rate is seen, while in the case of Pitressin the general pattern remains the same. 2) The initial slowing in the case of angiotensin depends upon the rise of blood pressure, and if this factor is reduced considerably there is no slowing.

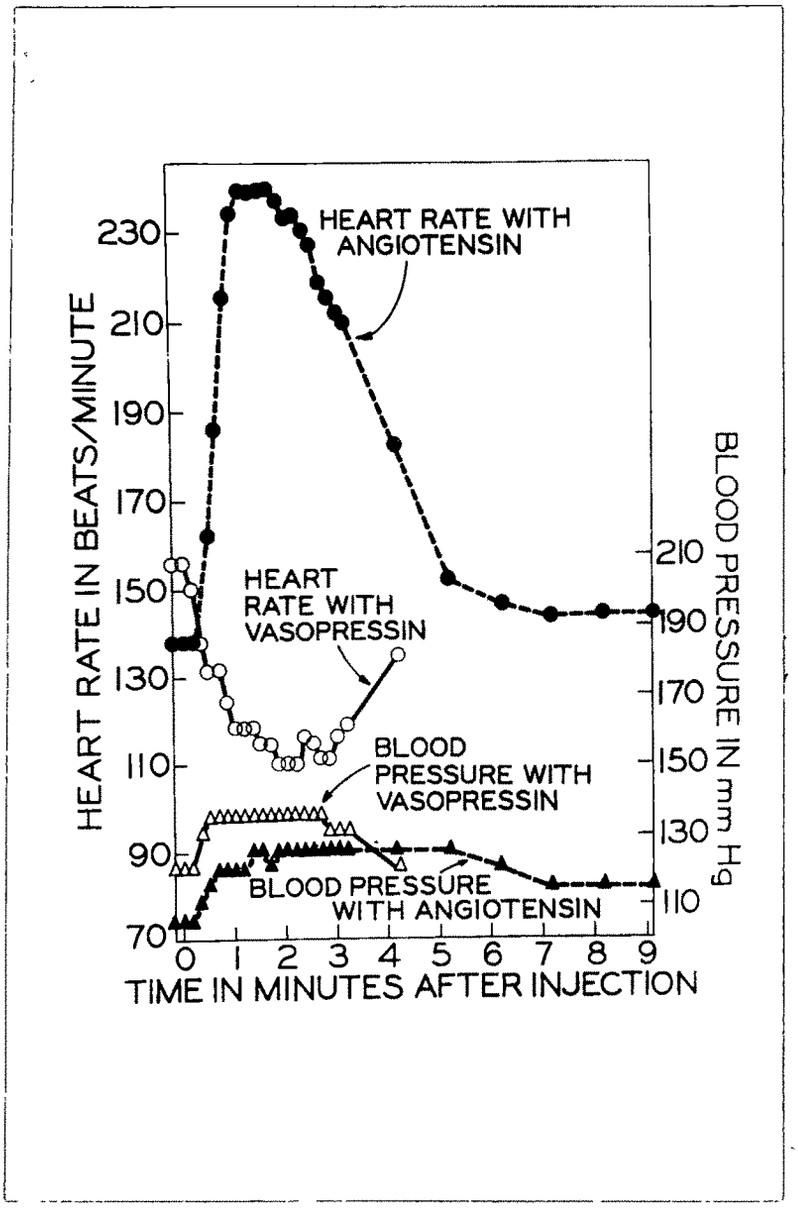

Fig. 3: Change in effect of angiotensin on heart rate produced by buffering the rise of blood pressure and its' comparison with Pitressin in the same dog.

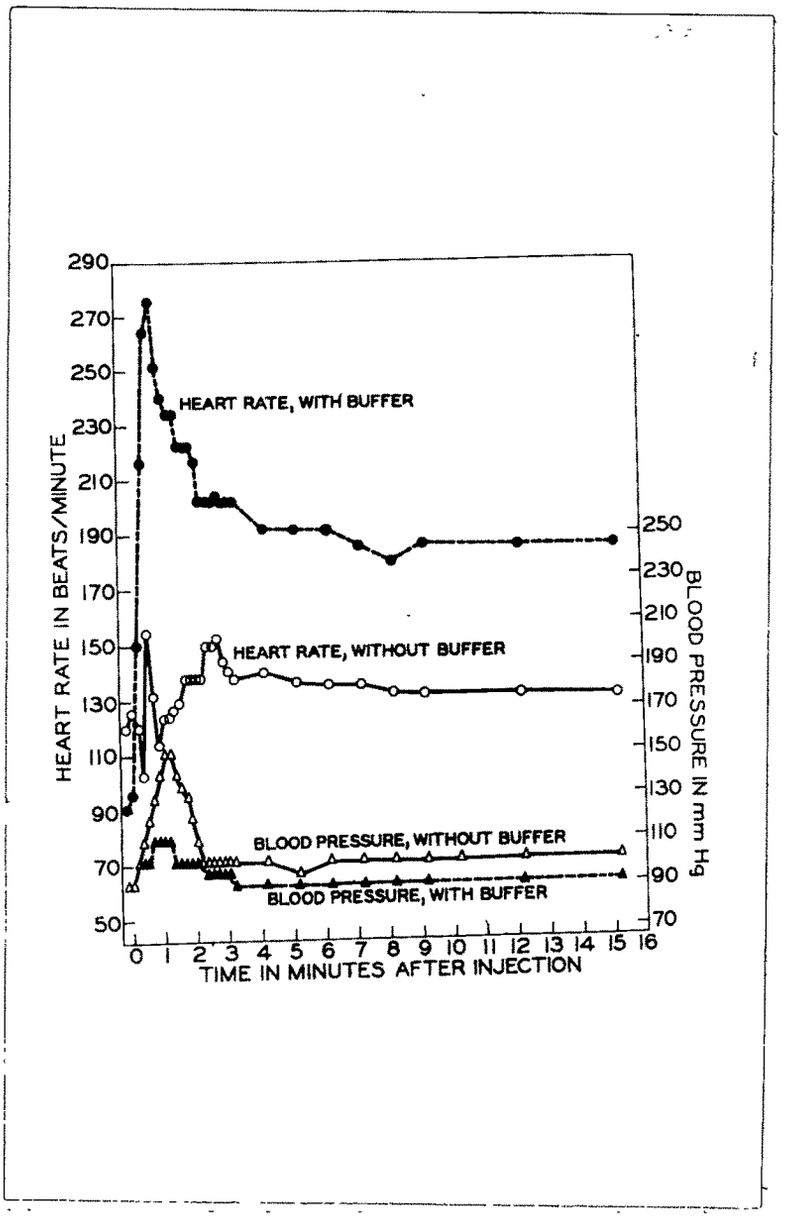

Fig.4: Effects of angiotensin (10 µg) on heart rate before and during buffering of pressor response.

Effect of slow administration of angiotensin

The relationship between rise of blood pressure and slowing of heart rate indicated that slow injection of angiotensin with the associated slow rise of blood pressure might fail to elicit cardiac inhibition. Angiotensin diluted (0.5 µg/ml) with 0.9% NaCl solution was injected by injecting machine. The administration of the drug was stopped when the blood pressure reached the peak and stayed there for awhile. On analysing Table 6 it is found that the maximum initial slowing with 5 µg angiotesnin per min. was about 30 beats/min., with 2.5 µg/min. it was 9 beats, with 3.8 µg/min. 3 beats and with 1.25 µg/min. it was either absent or negligible. Later a rise in heart rate was observed. The rise of blood pressure with the minimum dose of 1.25 µg/min. was around 30 mm.Hg.

These observations show that if the sudden rise of blood pressure is avoided by administering the drug slowly the initial cardiac slowing was proportionately less with the slower rates of infusion, until at the rate of 1.25 µg/min. the slowing did not occur (fig.5).

Angiotensin diluted as in previous experiments was infused initially at the rate of 0.63 µg drug/min. The heart rate and blood pressure were recorded.

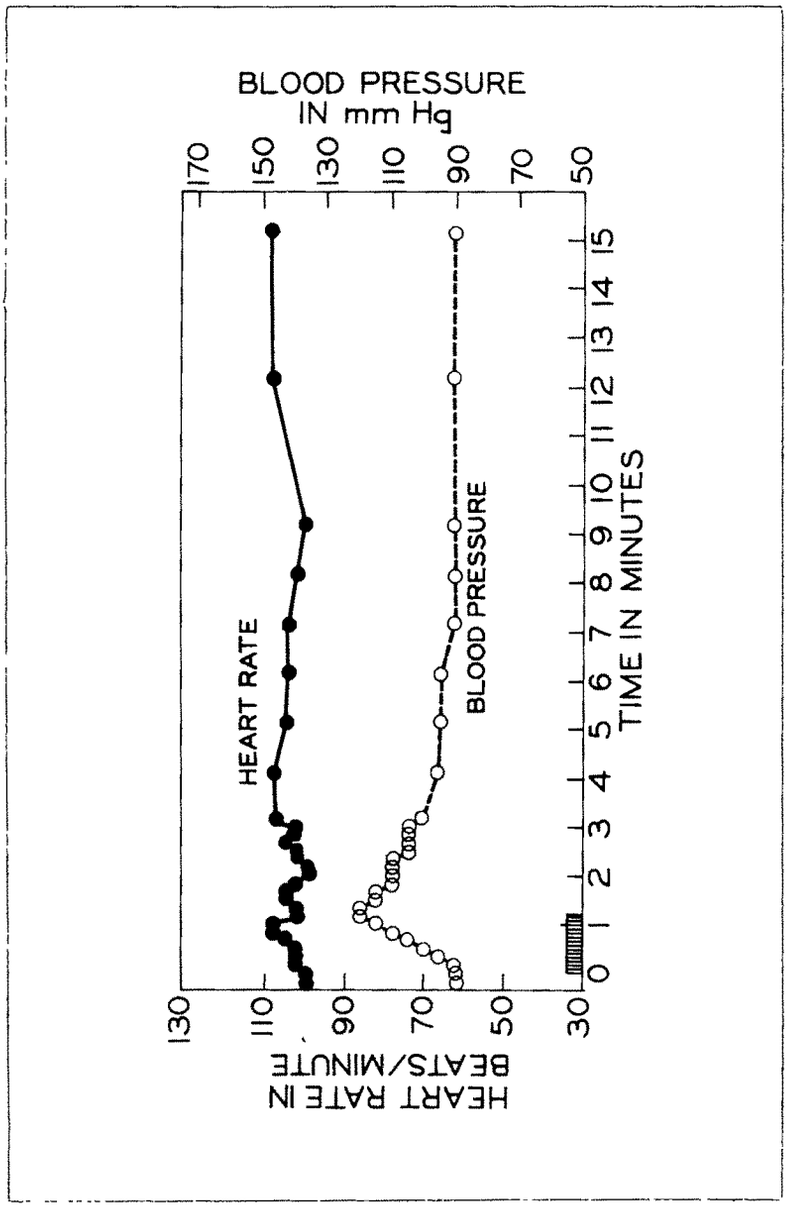

Fig. 5: Changes in heart rate and blood pressure during slow infusion of angiotensin (1.25 µg/min.).

As soon as the plateau of blood pressure was reached, the rate of infusion of the drug was doubled. The procedure was repeated with rates of 1.25, 2.5 and 5 µg/min. When the highest peak was reached with the last dose of drug the infusion was stopped (fig.6).

It is seen that with each increase of infusion rate there is a rise of blood pressure of around 25 mm. Hg. With the dose of 0.63 µg/min. there is no slowing (Table 6), with 1.25 µg/min. there is slowing of 3 beats/min., with 2.5 µg/min. a slowing of 6 beats/min. and with 5 µg/min. it was only 3 beats/min.

When these results of dog 16 are compared with corresponding similar doses in dog 15 a striking difference is observed. In this case, with the first dose of 0.63 µg/min. initial slowing is absent while a rise of 6 beats is present. With increasing doses the initial slowing appears but is very small in comparison with dog 15. The clearest difference is with the dose of 5 µg/min. In dog 15 the initial slowing with this dose is 30 beats/min. while in dog 16 it is only 3 beats/min. although the blood pressure increase is about three times in this case.

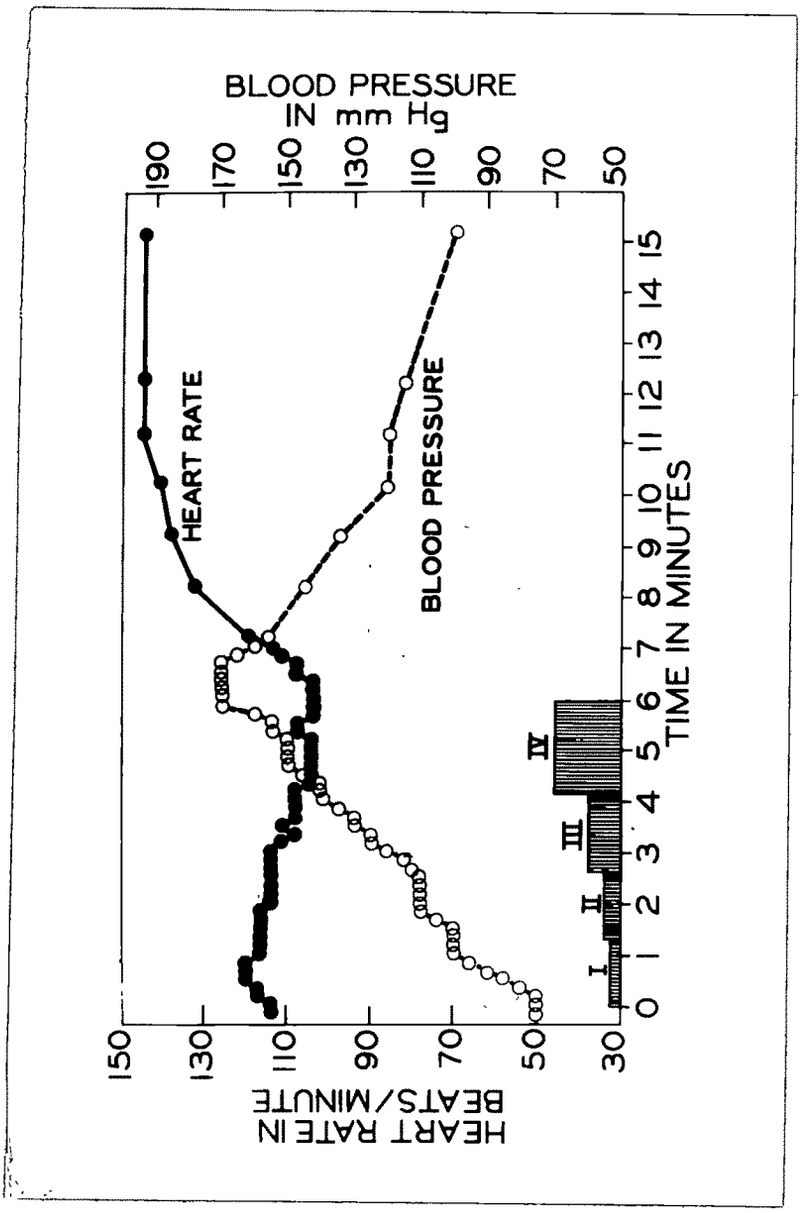

Fig.6: Effects on heart rate and blood pressure produced by progressively increasing the rate of injection of angiotensin:
I - Angiotensin 0.63 µg. per minute
II - Angiotensin 1.25 µg. per minute
III - Angiotensin 2.50 µg. per minute
IV - Angiotensin 5.00 µg. per minute.

Effect of vagotomy and carotid sinus inactivation on the cardioinhibitory response to angiotensin

Studies were performed on six dogs which were under the influence of morphine and chloralose. A control dose of 10 µg of angiotensin was administered intravenously and the results were recorded. Then the operation for sinoaortic denervation was performed and results of the same experiment were recorded. They are presented in Table 7 and fig.7.

After sinoaortic denervation the basal heart rate and blood pressure are at a higher level. When angiotensin was injected in such cases the heart rate and blood pressure rose. There was no cardiac slowing. The heart rate increased shortly after the beginning of the injection. The maximum increase in heart rate was about 80 beats/min. in all cases except one in which it was 40 (Table 8, dog 13).

In fig. 7 it is shown that heart rate continued to rise alongwith the rising blood pressure to reach a maximum, and then declined gradually.

This shows that if reflex effects from baroceptors cannot be elicited the rise of blood pressure is not accompanied by a decrease in heart rate. Under these

TABLE 6

EFFECTS ON HEART RATE AND BLOOD PRESSURE OF SLOW ADMINISTRATION OF ANGIOTENSIN

Dog No.	Rate of infusion of drug	Time in which blood pressure reaches plateau	Amount of drug infused	Basal heart rate	Maximum decrease in heart rate/min. after injection	Time for maximum decrease	Maximum increase in heart rate/min. after injection	Time for maximum increase	Maximum rise of blood pressure in mm.Hg.	Time for maximum rise
15	5 µg/min.	1:30	7.5 µg.	120	30	1:30	*	*	60	1:10
15	2.5 µg/min.	1:20	3.3 µg.	102	9	2:40	15	5:00	55	1:30
15	3.8 µg/min.	0:44	1.4 µg.	96	3	1:30	12	1:40	45	1:30
15	1.25 µg/min.	1:00	1.25 µg.	102	3	1:30	9	4:00	30	1:00
15	1.25 µg/min.	1:00	1.25 µg.	96	0	0	12	0:40	35	1:10
15	1.25 µg/min.	1:10	1.4 µg.	99	0	0	9	1:40	30	1:00
16	0.63 µg/min.	1:20	0.8 µg.	114	0	0	6	0:30	25	1:00
16	1.25 µg/min.	1:20	1.7 µg.	117	3	0:40	*	*	12	1:20
16	2.5 µg/min.	1:30	3.8 µg.	114	6	0:40	*	*	28	1:20
16	5 µg/min.	1:50	9 µg.	105	3	0:20	39	7:00	30	1:50

* Data not available.

TABLE 7

EFFECT OF SINOAORTIC DENERVATION ON THE CARDIOINHIBITORY RESPONSE TO ANGIOTENSIN

Dog No.	Angiotensin in μg.	Conditions of experiment	Heart rate in beats per minute at 10-second intervals after beginning of injections																
			-20	-10	10	20	30	40	50	1:00	10	20	30	40	50	2:00	3:10	4:10	9:10	12:10	15:10
11	10	Before SA denervation	72	72	72	60	57	60	60	57	69	72	72	72	84	84	90	84	90	87	87
11	10	After SA denervation	180	180	180	180	192	216	240	252	252	264	252	246	252	240	222	198	183	183	183
13	10	Before SA denervation	81	81	81	75	72	69	66	66	66	66	69	72	72	72	84	93	96	93	93
13	10	After SA denervation	230	230	23.	[illegible]	240	[illegible]	258	264	264	264	264	264	267	270	252	246	230		
14	10	Before SA denervation	70	70	70	66	66	60	50	45	45	45	54	60	60	60	72	72	90	84	78
14	10	After SA denervation	234	228	240	246	249	252	288	294	312	320	330	330	330	330	250	250	230	228	221

Dog No.	Angiotensin in units	Conditions of experiment	Heart rate before injection	Heart rate in beats per minute at 15-second intervals after beginning of injection									
				15	30	45	1:00	15	30	45	2:00	15	30
17**	30	After SA denervation	200	202	210	220	268	280	300	292	296	296	284
18**	30	After SA denervation	162	162	162	162	186	200	204	214	*	*	240
19**	30	After SA denervation	200	200	208	224	264	276	276	276	280	276	268

** Data were provided by Professor W.B. Youmans

* Data are not available.

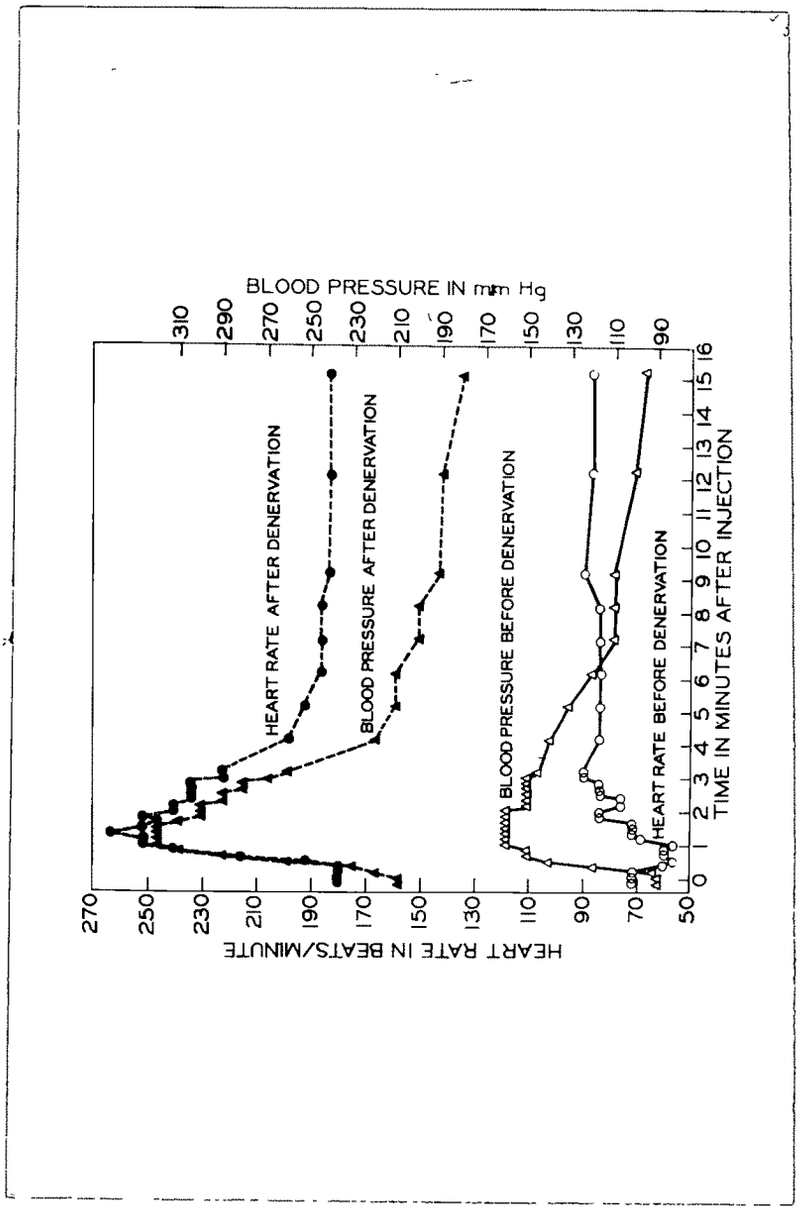

Fig. 7: Effects of angiotensin (10 µg.) on heart rate and blood pressure before and after sinoaortic denervation.

TABLE 8

EFFECT OF ANGIOTENSIN ON HEART RATE BEFORE AND AFTER SINOAORTIC DENERVATION

Dog No.	Amount of angiotensin	Condition of experiment	Rise in blood pressure in mm. Hg.	Basal heart rate/ min. before injection	Minimum heart rate/ min. after injection	Decrease in heart rate/min.	Maximum heart rate/ min. after injection	Increase in heart rate/min.	Time for maximum increase in heart rate
11	10 µg.	Before SA denervation	70	72	57	15	90	18	3:10
11	10 µg.	After SA denervation	110	180	180	0	264	84	1:20
13	10 µg.	Before SA denervation	80	81	66	15	96	15	9:10
13	10 µg.	After SA denervation	60	230	237	0	270	40	2:00
14	10 µg.	Before SA denervation	90	70	45	25	90	20	9:10
14	10 µg.	After SA denervation	50	231	240	0	330	99	1:30
17	30 µnits	After SA denervation	*	200	202	0	300	100	1:30
18	30 µnits	After SA denervation	*	162	162	0	240	78	2:30
19	30 µnits	After SA denervation	*	200	200	0	280	80	2:00

* Data are not available.

circumstances a cardioaccelerator action of angiotensin is demonstrated.

Comparison of the effects on heart rate by changing the sites of injection of angiotensin: The sites employed were femoral vein, femoral artery and common carotid artery

A dose of 10 μg was employed in each case. The time for the maximum rise of blood pressure to occur was less when the compound was injected into the femoral vein compared to the corresponding artery. Also, the initial slowing was less marked when the compound was injected into the arterial side.

When angiotensin was injected slowly, over a period of two minutes into the common carotid artery, the rise of blood pressure was gradual and prolonged and the initial slowing of heart rate was not seen and the increase in heart rate was more pronounced. Ten dogs were used for these experiments.

Comparison of the effect of angiotensin on heart rate in dogs with intact cardiac innervation, following vagotomy and following complete denervation of the heart

The control heart rate, after opening the chest, stabilized at an average of 170 beats per minute; after

vagotomy, the rate becomes 220 beats per minute. After passage of some time, the heart rate stabilized at an average of 190 beats/min. Following angiotensin, the heart rate increased and reached an average of 250 beats per minute. It then gradually declined to an average of 200 beats per minute. After bilateral sympathectomy, in which the sympathetic chain was removed from T_1 to T_6, the heart rate declined to an average of 165 beats per minute. If angiotensin was again injected, the heart rate increased to a lesser extent of about 10 beats per minute. Ten dogs were used for these experiments.

Effect of 10 µg. of angiotensin on heart rate as influenced by the (i) inactivation of the sinoaortic pressoreflexes, and (ii) complete transverse section of the spinal cord

After the injection of 10 µg. of angiotensin, the following response was obtained. A slowing of the heart rate was observed within two minutes after injection. This slowing was of the magnitude of 4 to 12 beats/minute with an average of 6 beats/minute. However, the heart rate returned to basal level and then showed an increase which usually was maximum eight to ten minutes

after the injection. This increase ranged from 12 to 39 beats/minute with an average of 20 beats/minute. The effect of a dose of 10 µg. of angiotensin was usually over after a period of about half an hour as shown by the return of heart rate and blood pressure to basal level. A few control doses of 1 ml of isotonic saline were injected, but in none of these cases was any change in heart rate or blood pressure observed.

On sinoaortic inactivation the initial slowing after the injection of angiotensin was not observed and subsequent increase in heart rate was more pronounced. This ranged from 18 to 88 beats with an average of 49 beats/minute. This average increase in heart rate in response to angiotensin injection after clamping of carotids and sectioning of vagi is more marked and statistically significant ($P = 0.05$) in comparison with the average increase in heart rate after angiotensin injection in intact animal.

When transverse section of the spinal cord was performed and the angiotensin was injected, the initial slowing of the heart rate was seen and this ranged from 12 to 30 beats/minute with an average of 20 beats (Table 9). The subsequent increase in heart rate was limited to an average of 9 beats per minute.

TABLE 9

CARDIAC ACCELERATOR EFFECT OF 10 µg. OF ANGIOTENSIN ON HEART RATE AS INFLUENCED BY THE (I) INACTIVATION OF SINOAORTIC PRESSOREFLEXES, AND (II) COMPLETE T. S. OF SPINAL CORD

Dog No.	Experimental conditions. 10 µg. of Angiotensin injected after following procedures	Basal Heart rate/min.	Minimum Heart rate/min after injection	Decrease in heart rate/min.	Average decrease in heart rate/min.	Maximum heart rate/min after injection	Increase in heart rate/min.	Average increase in heart rate/min.
40	Normal	132	120	12	-	156	24	20
41		126	114	12	-	144	18	
42		120	120	--	6	159	39	
43		160	155	5	-	174	14	
44		120	114	6	-	132	12	
45		118	114	4	-	136	18	
46		115	115	--	-	131	16	
47	Carotids clamped on both sides and both vagi sectioned.	183	185	--	-	240	57	49
48		96	138	--	-	132	36	
49		150	156	--	-	175	25	
50		120	120	--	-	150	30	
51		130	131	--	-	149	19	
52		132	132	--	NO	150	18	
53		115	116	--	-	190	75	
54		118	119	--	-	200	82	
55		97	97	--	-	130	33	
56		87	87	--	-	175	88	
57		120	122	--	-	200	80	
58	Vagi sectioned and transverse section of spinal cord performed.	120	108	12	-	118	10	9
59		150	120	30	20	130	10	
60		168	150	18	-	174	6	

Effect of angiotensin on heart rate after the blocking of autonomic ganglia and after the administration of sympatholytic compounds

The observed blocking effect of pentolinium as mentioned was tested by carotid sinus reflex and by stimulating the peripheral cut end of vagi. After the first dosage of pentolinium (5 mg/kg of body-weight, given intravenously in the femoral vein), the blocking effect was not fully observed, while the heart rate slowed after vagal stimulation (text fig.8) and the same increased in response to carotid sinus reflex. Subsequently, similar dosage of pentolinium was repeated upto four times, but complete blocking effect could never be observed.

When 10 µg of angiotensin was given after pentolinium, the initial slowing was absent or negligible in most of the cases, but subsequent increase in heart rate was present, which was quite pronounced in certain cases. It ranged from 17 to 102 beats/minute (Table 10) with an average of 60 beats/minute.

In certain cases, Serpasil was given in the dosage of 1 mg/kg of body-weight after pentolinium and was followed by the injection of angiotensin. Serpasil

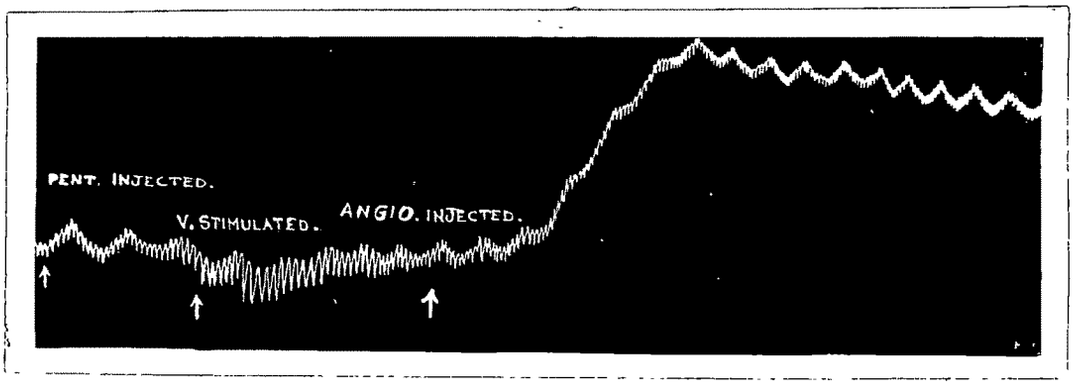

Fig.8: Effect of vagal stimulation and angiotensin (10 µg) on heart rate and blood pressure after the ganglia blocking by pentolinium (kymograph tracing).

TABLE 10

EFFECT OF 10 µg. OF ANGIOTENSIN ON HEART RATE AFTER THE BLOCKING OF AUTONOMIC GANGLIA AND/OR AFTER THE ADMINISTRATION OF SYMPATHOLYTIC COMPOUNDS

Dog No.	Experimental condition	Basal heart rate/minute	Minimum heart rate /minute after injection	Decrease in heart rate/ minute	Average decrease in heart rate/min.	Maximum heart rate/minute after injection	Increase in heart rate/min.	Average increase in heart rate/min.
61	10 µg. of angiotensin after pentolinium (20 mg/kg. of body weight).	115	114	1	--	132	17	60
62		96	96	-	--	198	102	
63		114	115	-	--	174	60	
64	Angiotensin after pentolinium and serpacil (1 mg/kg. of body weight).	144	144	-	--	198	54	32
65		120	120	-	--	150	30	
66		138	138	-	--	150	12	
67	Angiotensin after Bretylium tosylate (10 mg/kg. of body weight).	110	110	-	--	110	0	3
68		120	120	-	--	126	6	
69		128	128	-	--	130	2	
70		116	116	-	--	121	5	
71	Angiotensin after serpacil (1 mg/kg. of body weight).	150	150	-	--	150	0	3
72		134	134	-	--	142	8	
73		136	136	-	--	140	4	
74		120	120	-	--	120	0	

was given after pentolinium with the idea of having a blocking effect at autonomic ganglia and a sympatholytic effect at nerve endings. The acceleration effect was observed even on this occasion. This ranged from 12 to 54 beats/minute with an average of 32 beats/minute (Table 10).

In some other cases, pentolinium was not given, only bretylium tosylate was administered. In these situations, the injection of angiotensin brought about only slight acceleration effect of 3 beats/minute.

In the four dogs in whom only Serpasil was injected and the angiotensin followed this injeetion, it was observed that cardiac acceleration is very little and is of about the same magnitude as after bretylium tosylate (Table 10).

Effect of tying of the adrenal veins on cardiac accelerator effect of angiotensin

The average increase in heart rate/minute above basal level after injection of 10 µg of angiotensin is 31. When adrenal veins are tied and angiotensin is injected the same is 30. On statistical analysis it is observed that there is no significant difference between the increase in heart rate under the above

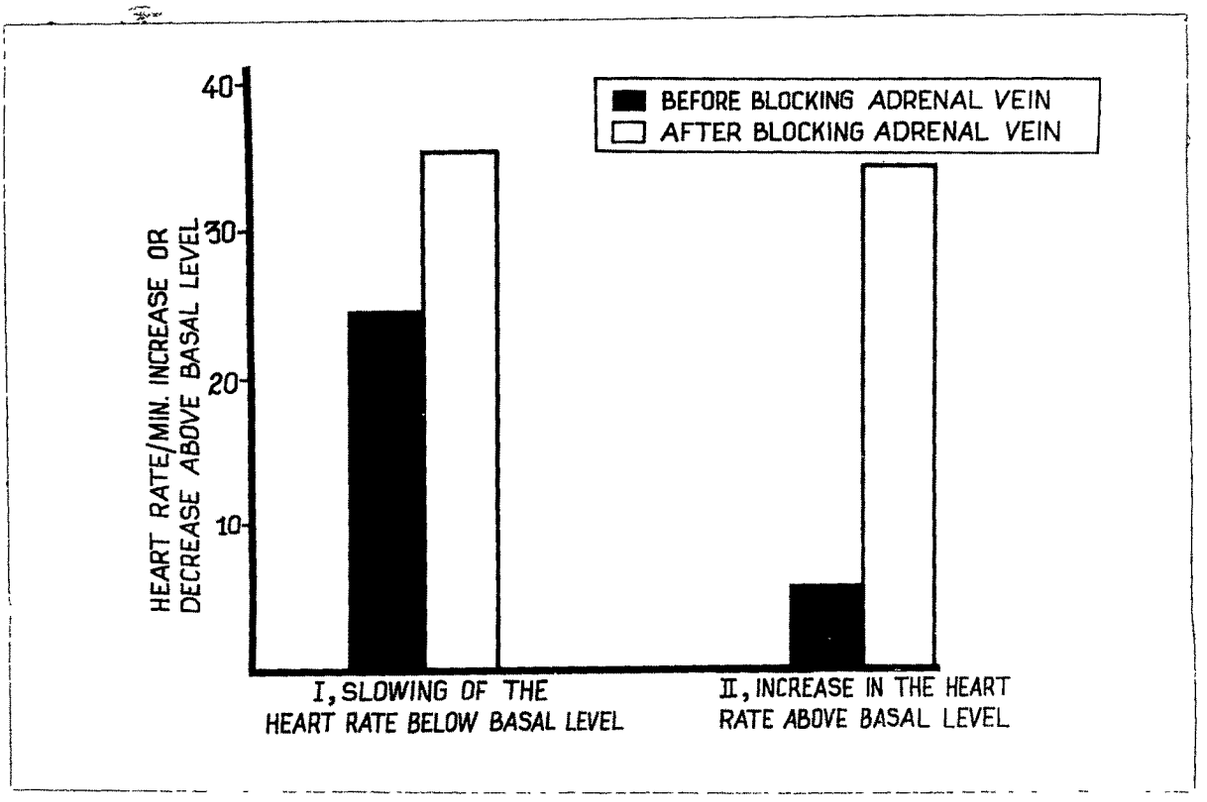

Fig. 9: Effect of angiotensin (10 µg) on heart rate before and after tying the adrenal veins.

TABLE 11

A COMPARATIVE STUDY OF THE EFFECT OF 10 μg. OF ANGIOTENSIN INJECTION ON HEART RATE OF THE SAME DOG BEFORE AND AFTER TYING THE ADRENAL VEIN

Dog No.	Experimental conditions	Basal H.R./min.	Maximum H.R./min. after injection	Increase in H.R./min.
55	A. Angio.	102	108	6
	B. Angio. After. Ad. Block	138	172	34
56	A. Angio.	174	206	32
	B. Angio. After Ad. Block	180	204	24
57	A. Angio.	114	162	48
	B. Angio. After Ad. Block	90	120	30
58	A. Angio.	180	204	24
	B. Angio. After Ad. Block	162	204	42
59	A. Angio.	132	176	44
	B. Angio. After Ad. Block	120	138	18

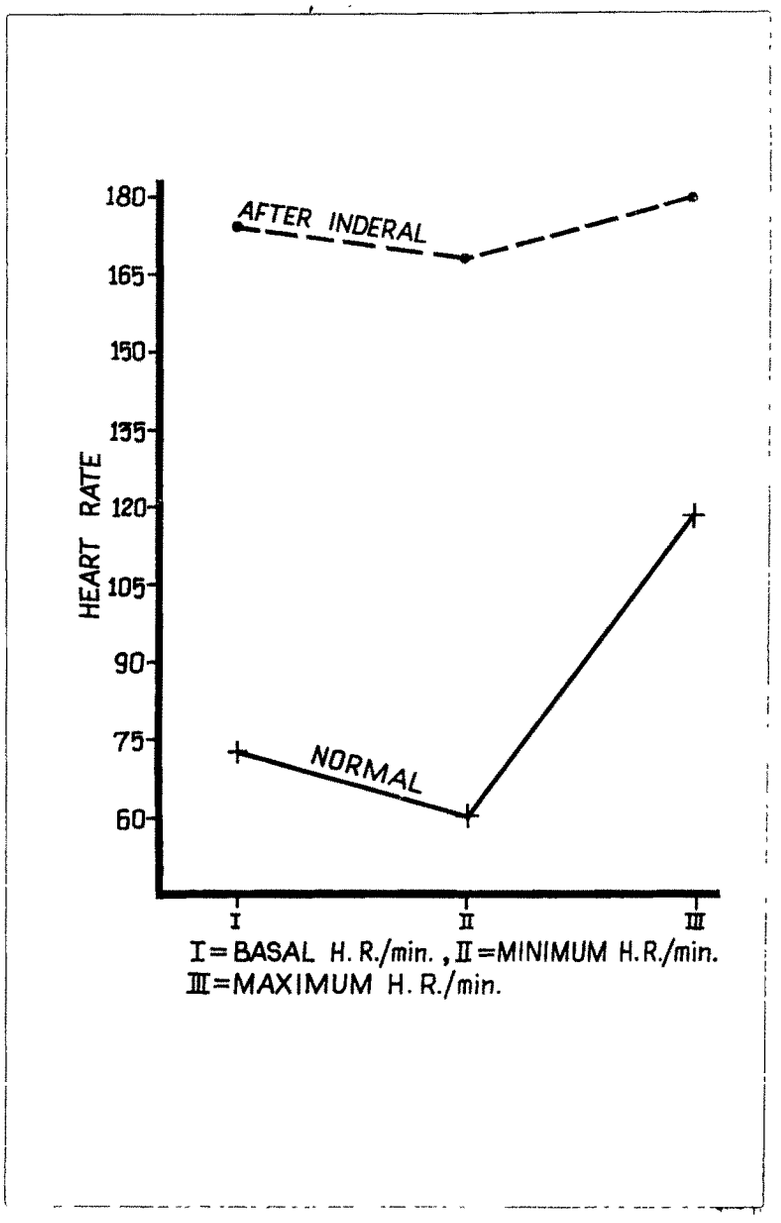

Fig. 10: Effect of angiotensin (10 µg) on heart rate after inderal.

TABLE 12

CARDIAC ACCELERATOR EFFECT OF 10 µg. OF ANGIOTENSIN ON HEART RATE AS INFLUENCED BY A PRIOR INJECTION OF INDERAL

Dog No.	Experimental conditions Following injected.	Basal H.R./min.	Maximum H.R./min.	Increase in H.R./min.
60	a. Angiotensin	240	262	22
	b. Angiotensin after Inderal.	174	180	6
61	a. Angiotensin	220	246	26
	b. Angiotensin after Inderal.	168	170	2
62	a. Angiotensin	72	118	46
	b. Angiotensin after Inderal.	174	178	4
63	a. Angiotensin	102	130	28
	b. Angiotensin after Inderal.	114	108	Below basal level.
64	Angiotensin after Inderal	126	126	0
65	Angiotensin after Inderal	138	143	5
66	Angiotensin after Inderal	192	168	Below basal level.
67	Angiotensin after Inderal	120	127	7

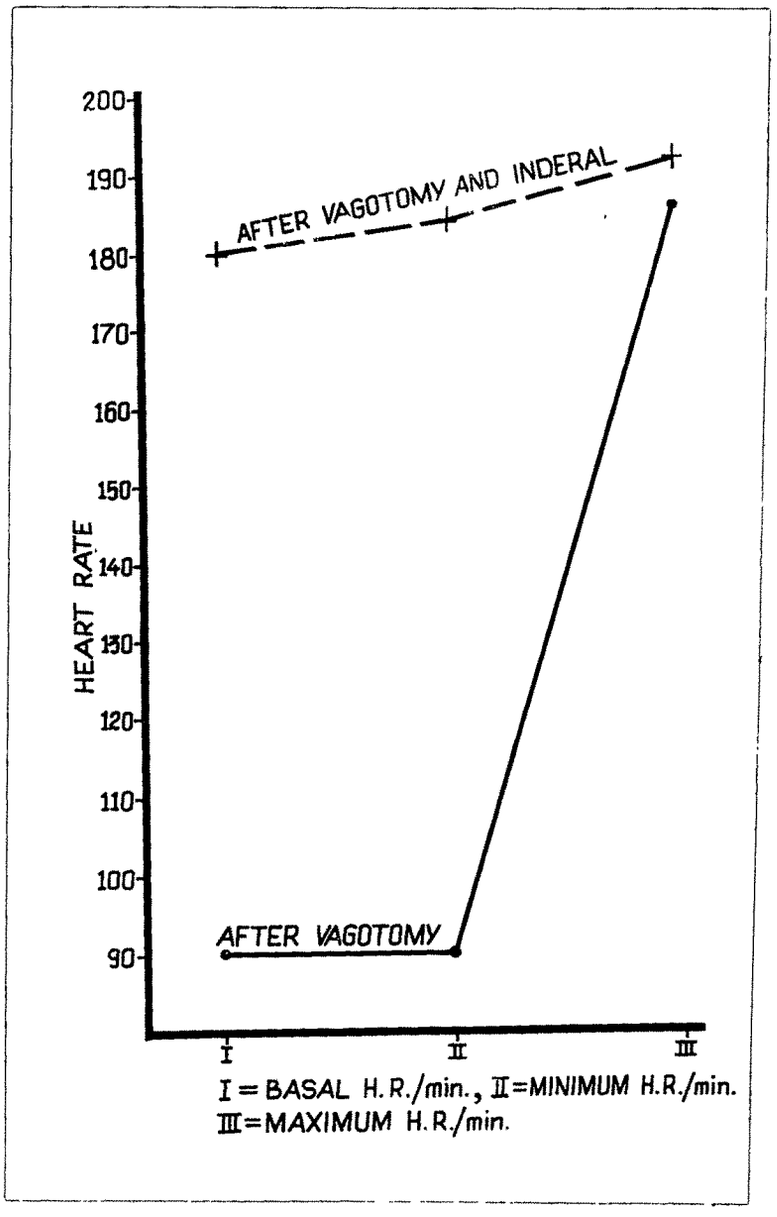

Fig. 11: Effect of angiotensin (10 µg) on heart rate after vagotomy and after vagotomy plus inderal.

mentioned two conditions (Table 11 and fig. 9 and 13). Tying of the adrenal veins does not have any effect on cardiac accelerator effect of angiotensin.

Cardiac accelerator effect of 10 µg of angiotensin on heart rate as influenced by a prior injection of inderal

The average increase in heart rate above basal level after injection of 10 µg of angiotensin is 29 (Table 12, fig.10 and 13). When angiotensin is injected after the injection of inderal, the same is nil. This difference in increase in heart rate is statistically significant (P = 0.01). Prior injection of inderal reduces the cardiac accelerator effect of angiotensin to a significant level. Vagotomy does not have any role in this (Fig. 11).

Cardiac accelerator effect of 10 µg of angiotensin on heart rate as influenced by a prior injection of reserpine

The average increase in heart rate above basal level after injection of 10 µg of angiotensin is 29 (Table 13, fig.12 and 13). When angiotensin is injected after the injection of serpasil the same is 5. This difference

TABLE 13

CARDIAC ACCELERATOR EFFECT OF 10 μg. OF ANGIOTENSIN ON HEART RATE INFLUENCED BY PRIOR INJECTION OF RESERPINE

Dog No.	Experimental conditions Following injected.	Basal H.R./min.	Maximum H.R./min.	Increase in H.R./min.
68	Angiotensin after Reserpine.	78	84	6
69	a) Angiotensin after Reserpine.	150	156	6
	b) Angiotensin after Reserpine.	170	168	N.O.
70	Angiotensin after Reserpine.	178	186	8
71	Angiotensin after Reserpine.	66	62	N.O.
72	a) Angiotensin after Reserpine.	54	60	6
	b) Angiotensin after Reserpine.	162	174	12
	c) Angiotensin after Reserpine.	138	144	6

N.O.; Not observed.

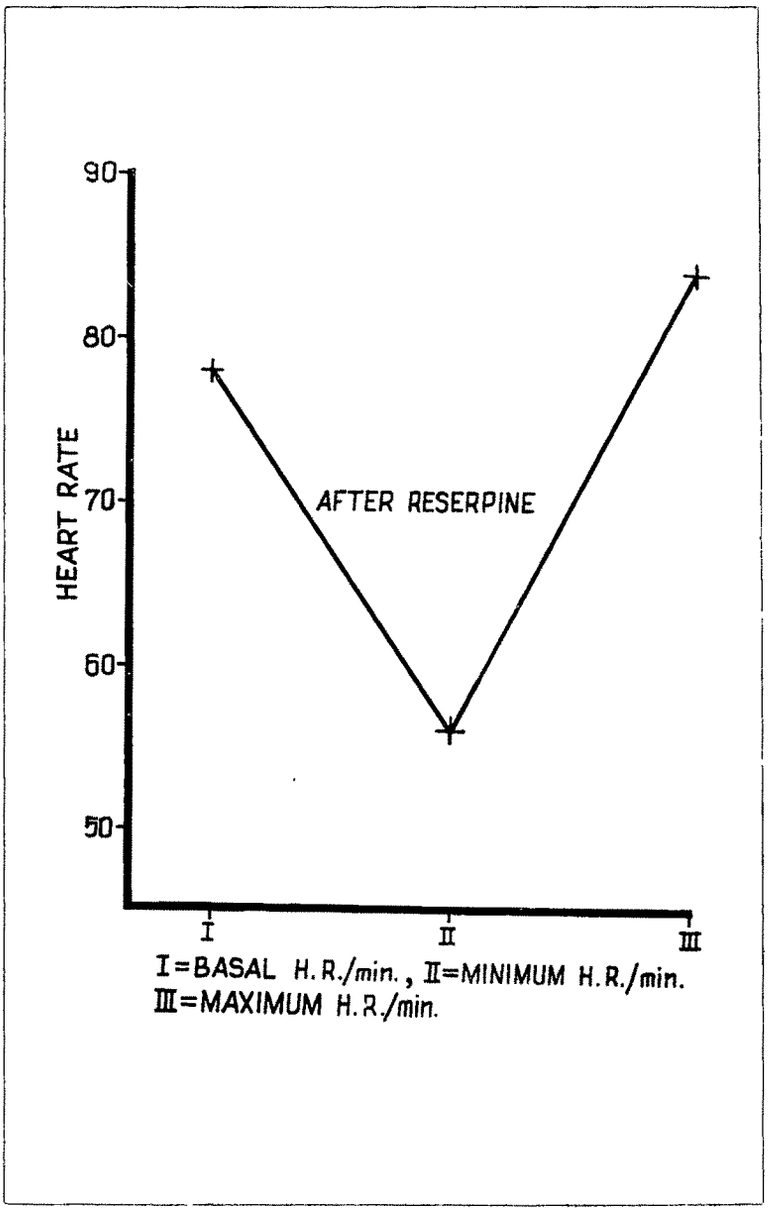

Fig. 12: Effect of angiotensin (10 µg) on heart rate after reserpine (2 - 3 mg/kg body weight).

in increase in heart rate is statistically significant ($P = 0.01$). This shows that prior injection of reserpine reduces the cardiac accelerator effect of angiotensin to a significant level.

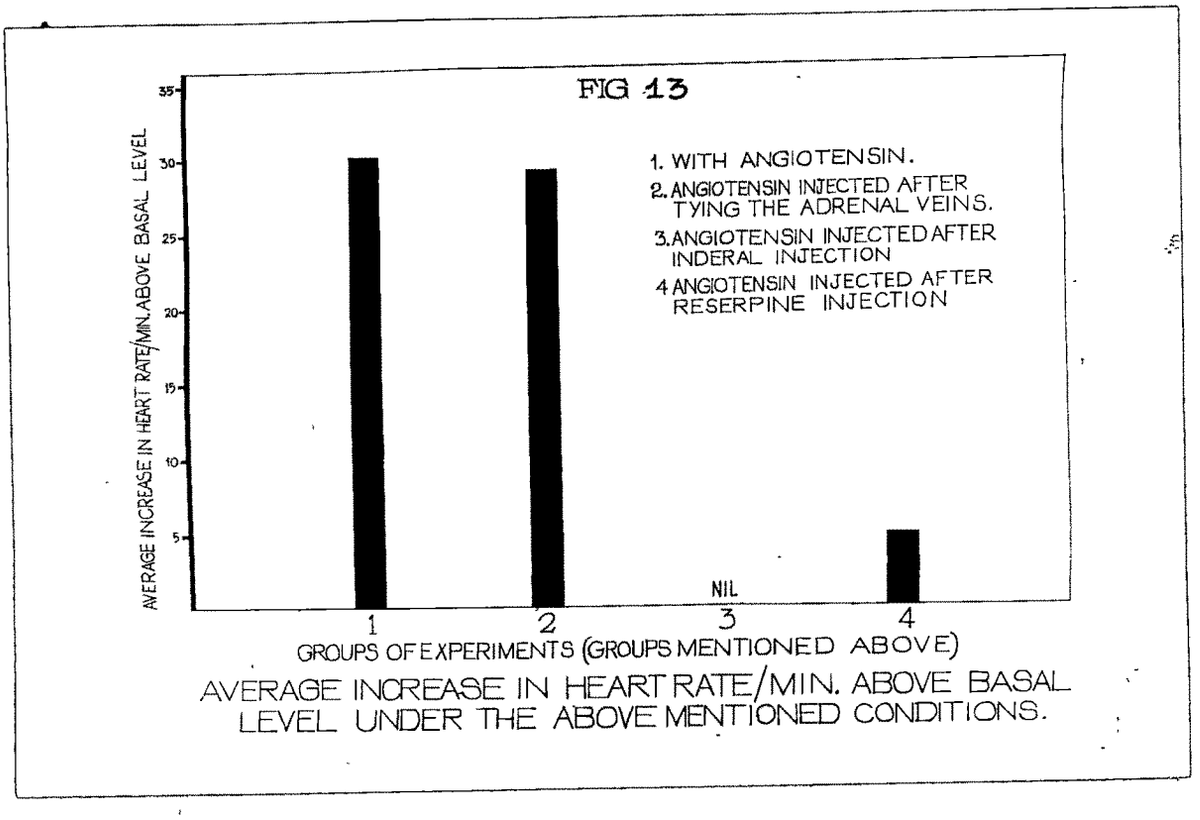

Fig. 13: A comparative study of effect of angiotensin (10 µg) on heart rate after,

a) tying adrenal vein, b) injection of inderal, and c) injection of reserpine.