A STUDY OF VENTRICULAR PRESSURE RECEPTORS AND THEIR ROLE IN THE BEZOLD REFLEX.

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STUDIES of reflex effects produced by injecting veratridine into the coronary arteries have yielded conclusive evidence for the existence of some kind of ventricular receptors [Dawes, 1947; Aviado, Pontius and Schmidt, 1949]. Investigations involving recording of impulses from cardiac afferent fibres have also provided some suggestive evidence [Amann and Schaefer, 1943; Jarisch and Zotterman, 1948; Dickinson, 1950; Pearce, 1951]. Whitteridge [1948] described four fibres with an early systolic discharge of impulses which began before the aortic valves opened and could not therefore have been set up by aortic pressure receptors. Later, Dickinson [1950] and Pearce [1951] also encountered such fibres. Whitteridge concluded that the receptors concerned were probably located in the ventricles.

Eleven fibres that also behaved in this way are described in the present paper. An experimental analysis of the conditions determining their discharge has shown that they originate in the ventricles, and the results obtained therefore confirm Whitteridge's earlier conclusion about the identity of such fibres. The effects of veratridine and veriloid on the activity of atrial and ventricular receptors have also been determined. These observations have provided valuable evidence of the role of these receptors in the Bezold reflex.

METHODS

Experiments were performed on 36 cats anæsthetized with chloralose (75 mg./kg.). The experimental procedure followed was the same as in the earlier investigations [Paintal, 1953 *a*, *b*].

A cardiac catheter (20 cm. long) was inserted into the right external jugular vein and it was so manipulated that its tip lay in the right atrium. A similar catheter was inserted directly into the right ventricle after opening the chest. Right atrial or right ventricular pressure was recorded with a capacitance manometer to which the appropriate catheter was connected. The frequency of the recording system including the catheter was 30–50/sec.; the manometer head itself had a much higher frequency. It was calibrated by means of a water manometer. Right atrial pressure and right ventricular pressure were each

recorded satisfactorily in 8 cats. A slow saline drip flowing through the catheter between recordings prevented blood from clotting in it.

Since the intracardiac pressure was recorded on one beam of a double-beam cathode ray tube and the e.c.g. and nerve impulses on the respective beams of another one, care was taken to ensure proper alignment of the three traces. This was done by photographing simultaneously for a short time the nerve impulses on both tubes along with the pressure and e.c.g. By this means any displacement of the beams of the two cathode ray tubes could be accurately measured.

To distend the ventricles or the atria, a balloon made of condom rubber tied to the end of a catheter was used. It was usually inserted through the apex of the ventricles.

The "veriloid" used was a commercial preparation for intravenous use manufactured by Riker Laboratories, Los Angeles, U.S.A. Each ml. was believed to contain 0·4 mg. of standard reference alkaloids of veratrum viride in 0·25 per cent of acetic acid. This was diluted with a solution of 0·9 per cent NaCl (w/v) to give a final concentration of 100 μg. of veriloid alkaloids/ml. Veratridine obtained from Professor Otto Krayer was dissolved in slightly acidified 0·9 per cent NaCl solution to give a final concentration of 10 μg./ml.

The carotid blood pressure was recorded on a kymograph by means of a conventional mercury manometer.

Results

Identification of Atrial and Ventricular Afferent Fibres.—Twenty-five atrial receptors including 7 right atrial type A, 8 right atrial type B, 2 left atrial type A and 8 left atrial type B were localized by a method already described [Paintal, 1953 *a*]. Additional evidence of the origin of 6 of these receptors was that they were stimulated by distending the appropriate atrium with a balloon [see Pearce, 1954], whereas distension of the adjacent ventricle did not arouse any of them. With 4 other atrial receptors it was observed, in confirmation of previous results, that their response to mechanical stimulation of the atrium was not affected by clamping the a-v junction, nor as shown in 6 other experiments were the receptors affected by removal of the ventricles (see fig. 10C). The survival of the atrial receptors under these conditions made it possible to establish with more certainty the origin of certain ventricular fibres.

Altogether 11 receptors have been located in the ventricles, 7 in the right and 4 in the left. The procedure for locating the ventricular receptors was in most respects similar to that used in locating the atrial ones. The fibre was first tentatively identified with the thorax intact. The thorax was then opened widely from a midline incision and the pericardium cut and removed. If it was found that occluding the pulmonary artery caused an increase in activity (see fig. 1B),

TABLE I.—SUMMARY OF CHARACTERISTICS USEFUL IN IDENTIFYING VARIOUS TYPES OF CARDIOVASCULAR AFFERENT FIBRES

Type of receptors	Main volley of impulses	Effect of inspiration on impulse activity	Effect of inflation on impulse activity	Return of activity after inflation	Response to veriloid
Right atrial type A Right atrial type B	Presystolic Late systolic	Increased early in inspiration	Reduced or abolished	Early	Not stimulated
Left atrial type A Left atrial type B	Presystolic Late systolic	Increased late in inspiration or beginning of expiration	,,	Late	Some are stimulated. Injection-reflex time > 20 sec. in great majority
Left ventricular	Early systolic in majority	Little or no change	,,	,,	All stimulated. Injection response time less than 15 sec. in great majority
Right ventricular	This terminates before mid-systole	,,	Indefinite	Indefinite	
Aortic pressure receptors	Begins early in systole but volley continues beyond mid-systole	Increased late in inspiration	Reduced or abolished	Late	Not stimulated

it was concluded that the fibre came from a receptor in the right side of the heart. The right a-v junction was then carefully occluded, and if this resulted in a reduction or abolition of activity (reversed by releasing the occlusion), then the fibre was taken to be a right ventricular fibre (fig. 1C). In all 7 fibres were identified in this way. Similar procedures were followed to identify left ventricular fibres. In their case, positive tests of identity were that a great increase in activity was produced by occluding the aorta (fig. 4) and a great reduction by clamping the left a-v junction.

In 3 of the right and 1 of the left ventricular fibres the impulse activity was abolished suddenly and irreversibly by clamping (with an artery forceps) the a-v junction. This was probably due to clamping the nerve fibres themselves. In this connection it is relevant to point out that Jarisch and Richter [1939] were able to abolish reflexes from the ventricles by carbolizing the ventricle just below the a-v groove.

In 4 ventricular receptors, 3 right and 1 left, positive evidence was obtained to prove that the receptors were actually located in the ventricles. In the case of two of these, the right ventricle was isolated *in situ* by carefully clamping the right a-v junction and pulmonary artery. In one of these the right ventricle was then distended by injecting saline into it, and the right atrium was widely slit so that it was completely collapsed. Pressing the ventricles now yielded an unmistakable response from the receptors. In the case of the 2nd fibre (fig. 1D), after observing the effect of pressing the right ventricle the apex was slit so as to collapse the ventricle; but responses from the receptor were still obtained by pinching the ventricular wall. However, when the incision was extended midway across the ventricle towards the base, responses from the receptor suddenly ceased, proving thereby that the receptor was definitely located in the right ventricle. In another experiment the ventral wall of the left ventricle was incised except along the a-v groove. By pressing the oval flap thus obtained between finger and thumb a clear discharge of impulses was produced. When the incision was extended along the ventricular side of the a-v groove the responses suddenly disappeared. In this way it was shown that the receptor was located in the left ventricular wall and not in the left atrium since, as already mentioned, atrial receptors survive removal of the ventricles.

All the fibres identified by these experimental methods as having their origin in the ventricles possessed the characteristics typical of ventricular receptors, which are listed in Table III. Altogether in the 36 cats experimented upon only 11 ventricular fibres were isolated. Their number must therefore be relatively small, since on an average it is customary to find quite easily about 6 to 10 active atrial fibres from the right vagus of one cat.

As indicated in Table I, the ventricular afferent fibres, unlike atrial

type B fibres [Paintal, 1953 *a*), were characterized by an early systolic burst of impulses. In 1 right and 2 left ventricular fibres this was followed by one or more impulses coincident with the decay of the T wave of the e.c.g. (fig. 1A). In 4 other ventricular fibres although there were no such impulses normally, they were produced by injection of saline into the right atrium, positive pressure inflation of the lungs, or during suction of air from the trachea. In one ventricular fibre only there was a presystolic burst of impulses. The main early systolic burst of impulses, however, was present in all fibres, and the time of its appearance was not much affected even by gross interference with the heart.

In 4 ventricular fibres, the first impulse of the main burst occurred between 20 and 33 msec. after the Q wave, and in 5 fibres between 40 and 60 msec. after the Q wave; in one fibre only it was delayed until 71 msec. after the Q wave. The peak frequency was attained between 25 and 70 msec. (between 25 and 50 msec. in 5 fibres, and between 55 and 70 msec. in 4 fibres) after the Q wave in all save one fibre. In this fibre, the one in which the onset of the discharge was the latest, the peak frequency was attained at 86 msec. after the Q wave. In these time relations the ventricular fibres differ from aortic depressor fibres in which the discharge is both later in onset and longer in duration. Similarly they differ from atrial type B fibres, which have a late systolic discharge that begins at 90 msec. or longer after the Q wave.

Except in the case of the one ventricular fibre with a delayed discharge, in which the main burst consisted of about 11 impulses, the systolic train of impulses numbered only 2 or 3 (4 fibres) or 4 to 6 (5 fibres). This is another way in which such fibres differed from aortic depressor and atrial fibres. In these the main burst of impulses was rarely less than 8 per cycle during inspiration.

The pattern of discharge in some ventricular fibres has been plotted in figs. 2, 3, and 8. Except for one right ventricular fibre (called RV_3 in fig. 2), the frequency plots for the several fibres are similar; RV_3 more nearly resembles an aortic depressor fibre. The pattern of discharge in some fibres was altered for a short while after the heart had been manipulated, *e.g.* by occluding a-v junction.

There was little or no evidence that respiration affected the normal behaviour of ventricular fibres. Of those observed at least 7 showed no respiratory variation in their discharge. Inflation of the lungs by positive pressure sometimes had no significant effect (5 RV and 1 LV fibres). On other occasions it reduced or abolished the normal discharge of active fibres (1 RV and 3 LV fibres); in the right ventricular one, peak activity returned in the first cardiac cycle after the end of inflation and in the left ventricular ones in the 5th or 6th cardiac cycle after inflation. This latter behaviour is similar to the return of activity in aortic pressure receptors after a maintained inflation [Whitteridge, 1948; Paintal, 1953 *b*].

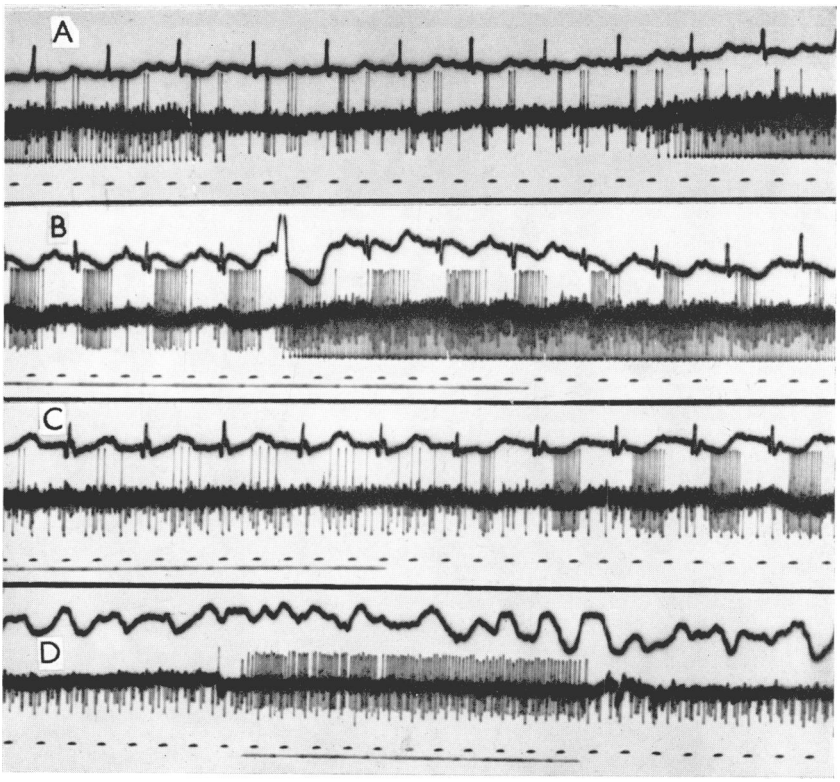

FIG. 1.—Impulses in a right ventricular fibre (large spiked fibre above baseline). A is a normal record with open chest and artificial ventilation. The large spikes below the baseline are from a pulmonary stretch fibre. B and C show respectively the effect of occluding the pulmonary artery and right a-v junction, end of signal indicates end of occlusion. In D the right ventricle was pressed during signal after clamping the pulmonary artery and right a-v junction. Responses from this fibre suddenly ceased when the ventricle was incised transversely across its middle. From above downwards in each record: e.c.g., impulses in fibres; time in 1/10 sec.; and signal.

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In no ventricular fibre did inflation of the lungs produce an increase in activity as was observed by Whitteridge in some of his fibres [Whitteridge, 1948].

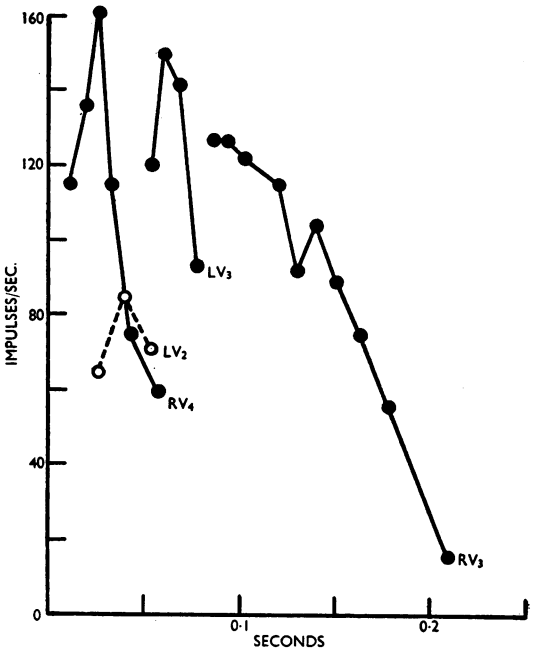

FIG. 2.—Graphs of frequency of impulses in different ventricular fibres. RV, right ventricular fibre; LV, left ventricular fibre. Time is measured from the Q wave of the e.c.g.

The effect of sucking air from the trachea was also unpredictable. This procedure either had no effect (1 RV and 2 LV fibres) or produced a small increase in activity. These results provide other differences of behaviour between ventricular fibres and aortic depressor or atrial fibres, both of which show well-marked respiratory changes in activity (see also Table I).

A marked increase in the frequency and duration of discharge in 10 ventricular fibres was produced by increasing the intraventricular pressure on the right side by occluding the pulmonary artery (figs. 1B and 3) and on the left side by occluding the aorta (fig. 4). The discharge of impulses began a little sooner and was continued till the end of the T wave, which marks the end of systole; and so it appears that under these conditions when the ventricular pressure rises greatly, the activity in the fibres follows the ventricular pressure. This is well illustrated in fig. 4. In fig. 3 the effect of occluding the pulmonary artery is shown. Although in this case the frequency of discharge was higher, the pattern was similar to the normal pattern of activity. Of the ventricular fibres

studied there was one right ventricular fibre which was unusual in exhibiting no change in activity during a rise in right ventricular pressure, but it was stimulated by distending the ventricle with a balloon. That this was a ventricular fibre was later ascertained when at the end of the experiment it was found to respond to pinching of a well-defined region of the right ventricle. Although this was a crude stimulus, it

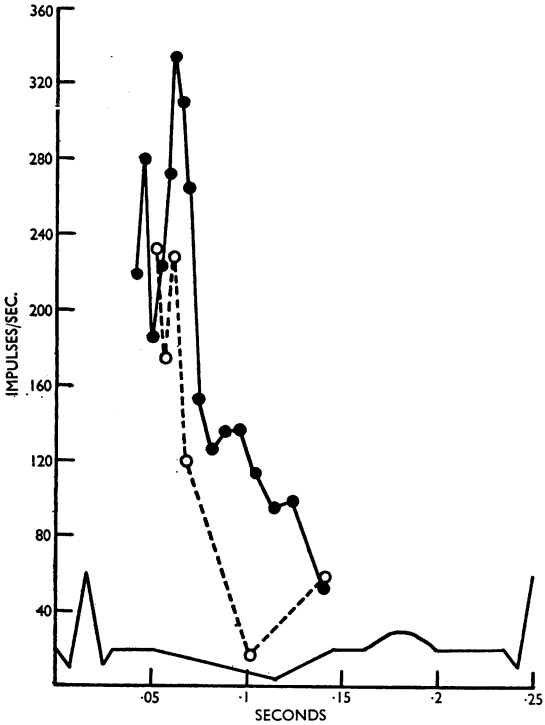

FIG. 3.—Graphs of frequency of discharge in a right ventricular fibre under normal conditions — — ○ — — ○ — — and while the pulmonary artery was occluded ——●——●——. Below, the e.c.g. Heart rate was the same in both cases. Time is measured from the Q wave of the e.c.g.

was useful as a rough guide in locating the situation of some ventricular receptors.

None of the fibres observed were stimulated by anoxia. It is unlikely, therefore, that any of them could have been chemoreceptors.

From a comparison of spike heights of ventricular fibres with those of pulmonary and other cardiovascular fibres whose conduction velocities are known [Paintal, 1953 *b*], it was concluded that the conduction velocities of the ventricular afferent fibres were of the order of 10–20 m./sec.; that is, it is probable that they are of the same size and have the same range of conduction velocities as atrial afferent fibres and belong, as do these, to the A group of sensory afferent fibres [Grundfest, 1940].

On the basis of other evidence [see Torrance and Whitteridge, 1948], one might expect that the ventricular fibres would cease to conduct at a temperature of 10° C.

In contrast to these ventricular fibres studied, atrial fibres showed the usual respiratory fluctuations in activity described earlier [Paintal, 1953 *a*]. These are indicated in Table I. This also summarizes the

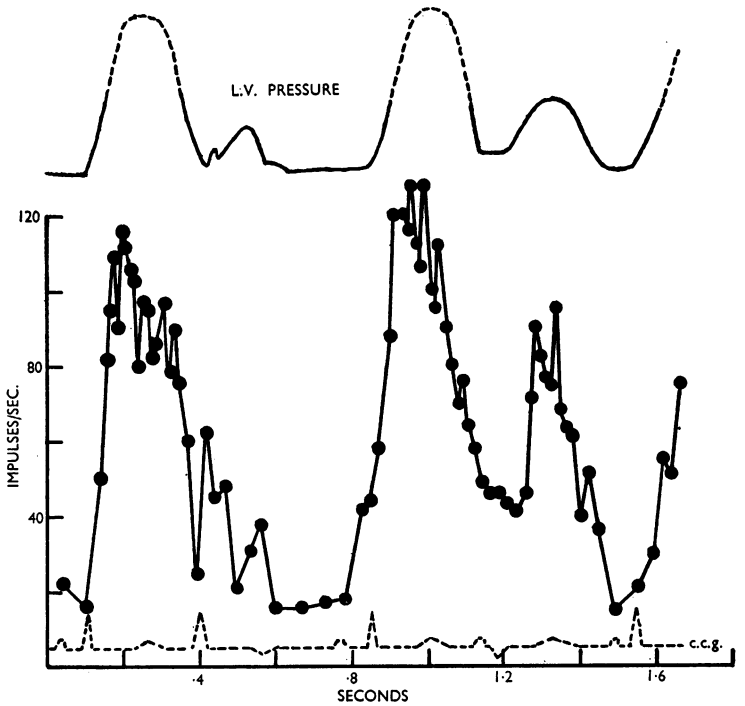

FIG. 4.—Graph of response in a left ventricular fibre during occlusion of the aorta. The pressure was recorded with a manometer that was much too sensitive. The interrupted portions of the pressure curve indicate the places where the great rise in pressure overshot the pressure registering limits of the manometer, solid part is a reproduction of original record. The e.c.g. is given below. Note the effect of extra systoles.

difference between right and left atrial fibres in their responses to inflation. One proved left atrial fibre was found to have an atypical response both to inflation and suction, *i.e.* the activity was diminished by suction and increased by inflation. The same fibre was also exceptional in exhibiting an early systolic discharge, which was also met with in one other left atrial fibre. It should be noted that the e.c.g. was normal in both cases, so that the early systolic discharge could not be accounted for as was that of other atrial fibres seen in this and in earlier studies by Whitteridge [1948] and Dickinson [1950], when the heart had a nodal rhythm. Left atrial fibres with an early systolic discharge

TABLE II.—RESPONSES OF VENTRICULAR AND LEFT ATRIAL RECEPTORS TO INJECTION OF ABOUT 200 μG. VERILOID AND 22 μG. VERATRIDINE INTO THE RIGHT ATRIUM

Weight of cat in kg.	Serial number of receptor	Drug	Injection-response time in fibres in sec.	Time to reach peak stimulation after injection in sec.	Duration of stimulation	Lowest frequency of impulses during maximal stimulation	Peak frequency/Lowest frequency	
							During maximal stimulation	During other states
2·8	RV_2	Veriloid	9·0	14·0	15 min. (approx.)	79	1·7	15 while occluding pulmonary artery
1·7	RV_3	,,	9·5	14·0	1 min. (approx.)	92	2·2	8 while occluding pulmonary artery
2·5	RV_4	,,	7·5	14·0	10 min. (approx.)	60	1·2	3 † while occluding pulmonary artery
2·3	LV_1	,,	14·5	32·0	10 min. (approx.)	44	1·1	8·0 while occluding aorta
2·6	LV_2	,,	11·0	19·0	2 min. (approx.)	22	2·8	5 ,, ,, ,,
4·0	RV_5	,,	8·0	13·0	10 min. (approx.)	43	1·2	7 normal
3·5	RV_6	Veratridine	5·6	7·0	9·2 sec.	49	1·4	17 while occluding pulmonary artery
3·7	RV_7	,,	5·2	8·0	18·0 sec.	38	2·4	17 normal
3·0	LV_3	,,	7·3	9·0	5·3 sec.	93	2·0	48 ,,
	LV_3	,,	5·2	9·0	9·4 sec.	62	2·4	
4·0	LV_4	,,	6·5	7·5	2·5 sec.	15	6·0	6 while occluding aorta
	LV_4	,,	6·2	7·0	1·2 sec.	15	2·5	
3·2	LAB_2	Veriloid	30·0	46·0	10 min.	56	2·4	7 while occluding left a-v junction
	LAB_2	* ,,	19·0	30·0	?	58	1·3	
2·5	LAA_1	,,	60·0	70·0 (approx.)	4 min. (approx.)	96	1·3	23 normal
2·5	LAB_4	,,	70·0	?	4 min. (approx.)	82	1·5	10 while occluding left a-v junction
	LAB_4	* ,,	60·0 (approx.)	?	1 min. (approx.)	39	1·9	
3·2	LAB_6	Veratridine	8·0	10·0	1·5 min.	88	1·2	3 while occluding left a-v junction
	LAB_6	* ,,	8·0	11·0	4 min. (approx.)	81	1·1	

* Drug injected into left ventricle. † Receptor was still sensitized by veriloid when the pulmonary artery was occluded.

RV = Right ventricular receptor.
LV = Left ventricular receptor.
LAA = Left atrial type A receptor.
LAB = Left atrial type B receptor.

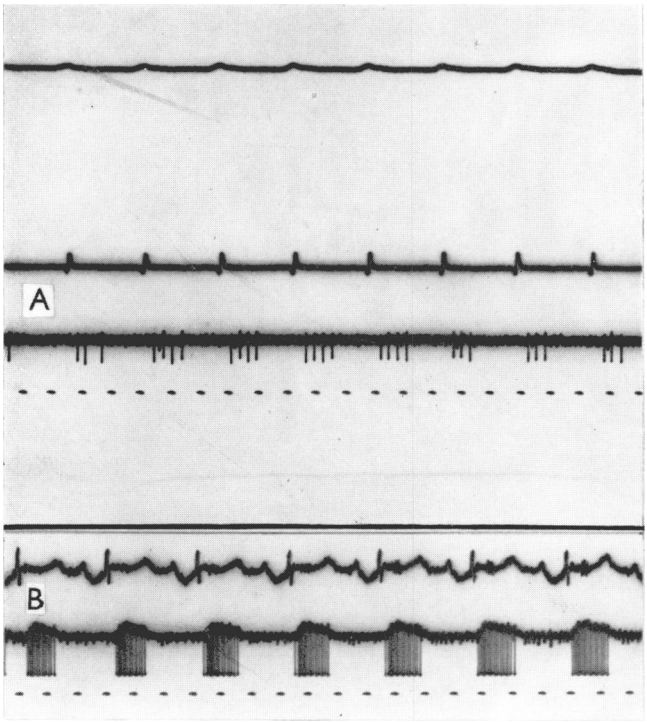

FIG. 5.—Early systolic burst of impulses in two left atrial fibres. In both the e.c.g. is normal, and in A the *a* wave of the pressure curve precedes the discharge. From above downwards: right atrial pressure; e.c.g.; impulses in a fibre; time in 1/10 sec.; and intrapleural pressure. There are no records of atrial or intrapleural pressure in B.

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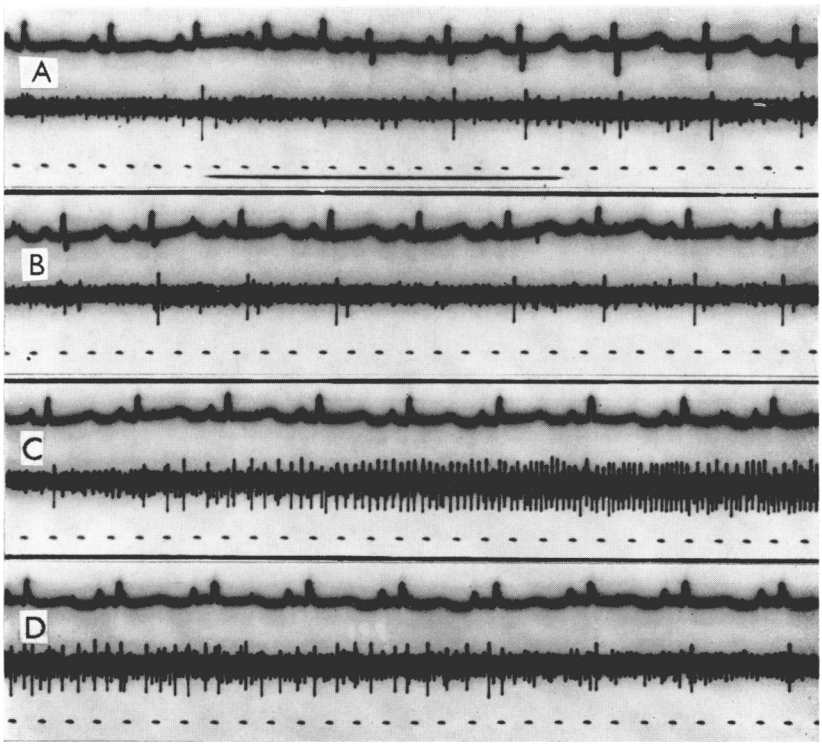

FIG. 6.—Response in a right ventricular fibre (large spike) following injection of 22 μg. veratridine into the right atrium at signal in A. Records A, B and C are continuous. Injection-response time is 5·6 sec. D was recorded 5 sec. after C. From above downwards: e.c.g.; impulses in a fibre; time in 1/10 sec.; and injection signal in A.

(fig. 5) though uncommon can be confused with ventricular fibres, as no doubt happened in two experiments until removal of the ventricles proved that the receptors were located in the left atrium.

TABLE III.—SUMMARY OF RESPONSES FOLLOWING INJECTION OF VERILOID AND VERATRIDINE INTO THE RIGHT ATRIUM

	Drug	Number of fibres	Range	Mean	S.D.
Responses in ventricular fibres					
Injection-response time	Veriloid	6	8–15 sec.	10 sec.	2·3
	Veratridine	6*	5–7 sec.	6 sec.	8·8
Time to reach peak stimulation	Veriloid	6	13–32 sec.	18 sec.	6·7
	Veratridine	6*	7–9 sec.	8 sec.	0·8
Duration of stimulation	Veriloid	6	1–15 min.	8 min.	1·4
	Veratridine	6*	1–18 sec.	8 sec.	5·5
Responses in left atrial fibres					
Injection-response time	Veriloid	5†	19–70 sec.	48 sec.	20
Time to reach peak stimulation	Veriloid	3	30–70 sec.	..	..
Duration of stimulation	Veriloid	3	4–10 min.	..	..
		Number of cats			
Reflex bradycardia					
Injection-reflex time	Veriloid	8	6–11 sec.	8 sec.	1·4
	Veratridine	8	5–8 sec.	6 sec.	1·1
Time for peak bradycardia	Veriloid	6	10–24 sec.	20 sec.	4·9
	Veratridine	7	9–20 sec.	16 sec.	4·1
Duration of bradycardia	Veriloid	6	0·5– > 4 min.	..	..
	Veratridine	7	0·5– > 4 min.	..	..

* 6 observations in 4 fibres.
† 5 observations in 3 fibres.

RESPONSES OF THE VENTRICULAR AND ATRIAL RECEPTORS TO VERILOID AND VERATRIDINE

All the ventricular receptors and some left atrial ones were strongly stimulated by veriloid and veratridine (figs. 6–10). In experiments in which these drugs were studied the relevant intracardiac pressures were not recorded, so that the extent to which the receptors were sensitized and/or stimulated cannot be evaluated precisely. The increase in the lowest frequency of discharge of a given fibre brought about after administration of the drug was taken as one criterion of the action of the drug on the receptors. This was more meaningful when considered in relation to peak frequency of discharge at the time; and so the ratio peak frequency : lowest frequency of discharge has been tabulated (see Table II) for all fibres showing an increase in discharge in response to veriloid or veratridine. For comparison, Table II also includes figures for the ratio without experimental interference (entered as "normal" in the table), and while occluding either the right or left a-v junction,

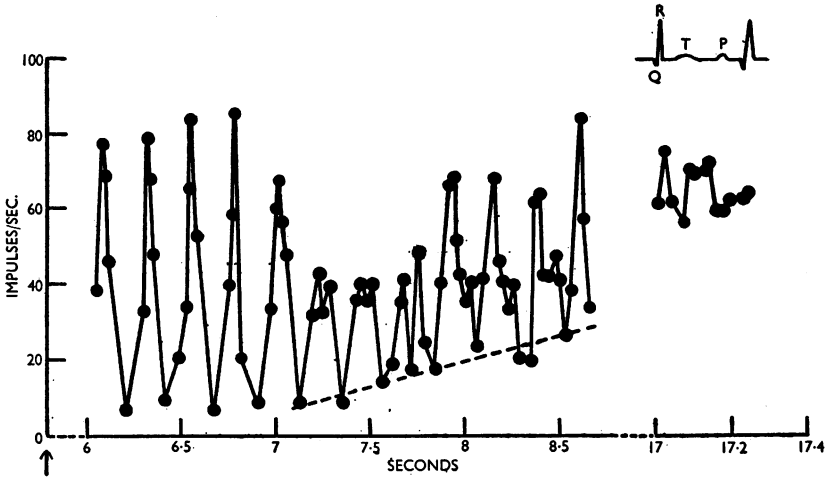

FIG. 7.—Graph of frequency of discharge in a right ventricular fibre following injection of veriloid into the right atrium at arrow (zero time). Note the gradual stimulation of the receptor as shown by the rise in the lowest frequency of discharge indicated by the interrupted line.

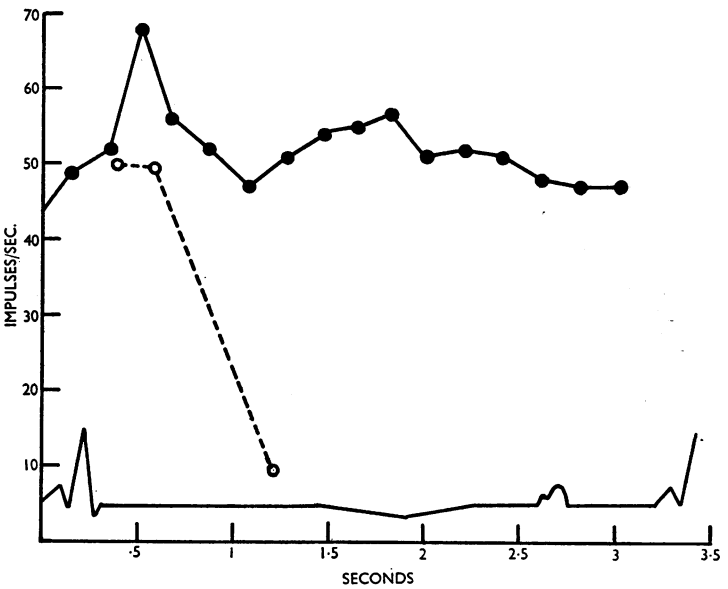

FIG. 8.—Graph of frequency of discharge in a left ventricular fibre at the height of stimulation by veriloid ——●——●——. A plot of the frequency of discharge before the drug — — ○ — — ○ — — shows that the peak frequency is not much affected and that its relation to the e.c.g. is not altered although the receptor is greatly stimulated by veriloid. Time is measured from the beginning of Q wave of the e.c.g.

or the pulmonary artery or the aorta. These show that the response to the drugs estimated in the above manner is much greater than any effect which can be produced by pressure changes within the heart.

The fall in the value for the ratio peak frequency : lowest frequency reflects chiefly a rise of the lowest frequency. The effect was to convert a rhythmic discharge into a nearly continuous one; a cardiac rhythm might still be discernible (fig. 8), but it might disappear with the great increase in discharge during diastole (fig. 10B), and in some cases a slight reduction of systolic discharge (*i.e.* the peak frequency fell off). This was further reason for believing that the receptors were being excited directly by the drugs, since they were firing off at a time when they would usually be silent.

Both Tables II and III indicate the main differences in the effects of the two drugs used. This is, that the action of veriloid was slower in onset and longer lasting than veratridine. These results are statistically significant.

There was evidence that each of the drugs was to some extent selective in action. Both stimulated the ventricular fibres, neither stimulated any of the 10 proved right atrial fibres; while the latent period of stimulation for the left atrial fibres, about a third of which responded to the drugs, was significantly longer than that recorded for the right ventricular fibres. This value, called the injection-response time in Tables II and III, indicates the interval between the beginning of the injection and the beginning of the response in the fibre. This was easily reckoned in most fibres by the sudden onset (within one to two beats) of a continuous discharge (figs. 6 and 10). In others, action on the receptors took place gradually (see figs. 7 and 9); in such cases the beginning of the response was determined from the beginning of the gradual rise in the lowest frequency of discharge.

The responses to both drugs were depressed by urethane (25 per cent solution), which when injected intravenously prevented or cut short the response to either of the drugs. The responses to veratridine itself could be observed a second time if an injection of the drug were made again 5–10 min. after the first. The second response was similar in its time-course to the first (*cf.* Table II, LV_3, LV_4, LAB_6).

The interval between the beginning of the injection and the beginning of reflex bradycardia was determined in 16 experiments. This reflex cardio-decelerator time for veriloid was found in 8 cats to be between 6–11 sec. (mean, 8 sec.; S.D., 1·4 sec.). In 8 other cats the corresponding time for veratridine was 5–8 sec. (mean, 6 sec.; S.D., 1·1 sec.). Using veratridine, Aviado, Pontius and Schmidt [1949] obtained similar figures in the dog. These times are significantly shorter than those obtained after veriloid. The time-course for reflex bradycardia in response to each of the two drugs is indicated by the data given in Table III.

Veriloid also tended to act more slowly in causing a fall in blood

pressure. In 3 cats the vasodepressor effect of the drug appeared 11, 11 and 5 sec. respectively after injection, while after veratridine in 2 cats it appeared after 5 and 7 sec. These figures agree with those obtained by Moe, Bassett and Krayer [1944] and Aviado *et al.* [1949] in the dog with veratridine.

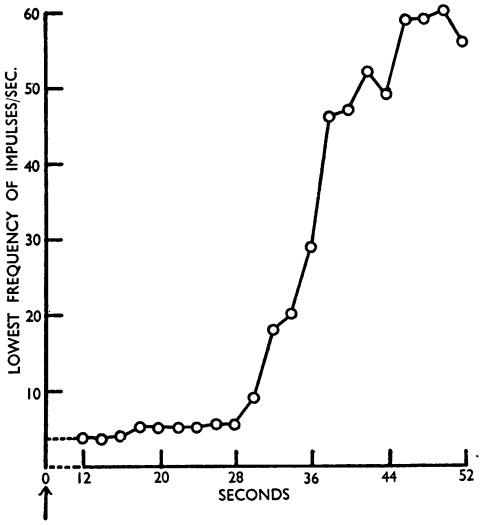

FIG. 9.—Graph of the lowest frequency of discharge in a left atrial type B fibre after injection of veriloid into the right atrium at arrow (zero time).

DISCUSSION

The majority of the ventricular receptors encountered were pressure-sensitive. It is certain that some of them were excited early in the isometric phase of ventricular contraction, others during the ejection phase, when intraventricular pressure rises to a peak. These differences can be explained by assuming that the thresholds of pressure at which the receptors are excited varies from one receptor to another. An interesting point is that the discharge ceases in most receptors before the peak pressure in the ventricles is reached, which occurs at least 100 msec. after the Q wave. This may be due to adaptation of the receptor or shortening of the muscle elements which may mechanically inhibit the receptors; perhaps both factors are operative.

The reflex functions of the ventricular receptors may be deduced from the reflex effects of veriloid and veratridine as shown in Table III, and by the results of Moe *et al.* [1944]. These observations indicate that the afferent mechanism concerned should be stimulated about 6 and 8 sec. after veratridine and veriloid respectively, and since the mean injection-reflex times of these drugs are significantly different, there should also be a significant difference in the time required to stimulate the receptors

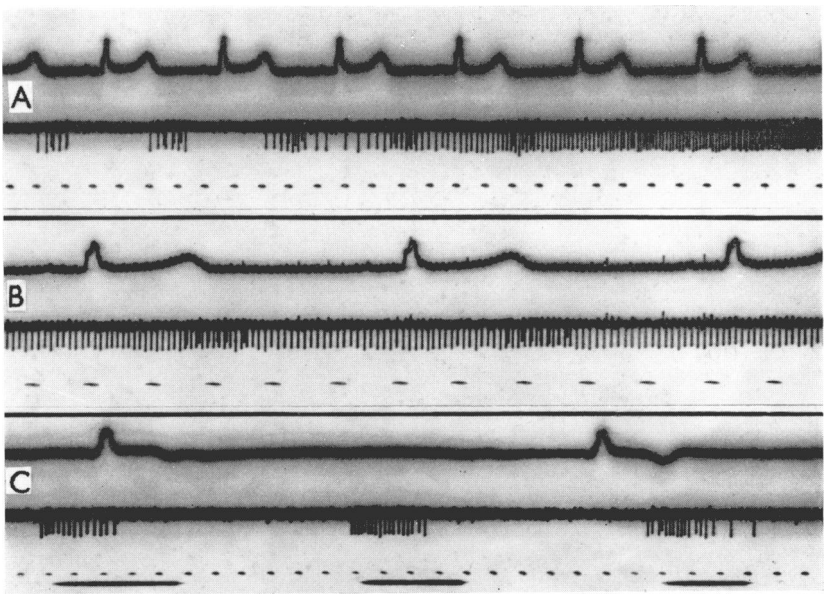

FIG. 10.—Impulses from two left atrial type B receptors following injection of 22 μg. veratridine into the right atrium 6·8 sec. before beginning of record A. B recorded 5·6 sec. after A; note that the fibre with the smaller spike is unaffected. C shows the response of the receptor stimulated by veratridine to touching a part of the left atrium after cutting away the ventricles.

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by the two drugs respectively. Further, peak stimulation of the receptors should occur by about 16–20 sec. after both drugs, as the peak fall in heart rate occurs by that time. The ventricular receptors satisfy these requirements. The left atrial receptors cannot be responsible for the initiation of the reflex following veriloid, because by the time they are stimulated peak bradycardia has already occurred (Table III).

An interesting point is that the duration of stimulation of ventricular receptors by veratridine is about 1–18 sec. (mean, 8 sec.; S.D., 5·5 sec.), so that if the bradycardia of veratridine is produced only by the activity of ventricular receptors, then the bradycardia should cease by this period. But it continues for a much longer time, *i.e.* 0·5 to > 4 min., so that other mechanisms must also be involved; a central one is not unlikely. But since Krayer, Wood and Montes [1943] have shown that the bradycardia of cardiac origin in the dog lasts for several minutes, the responses of left atrial receptors to veratridine may account for the prolonged duration of bradycardia (Table II). It is therefore concluded that the ventricular receptors start the bradycardia, and that this is augmented by the stimulation of left atrial receptors.

Since the interval between the injection of veriloid and the beginning of the fall in blood pressure in cats was 5–11 sec., the left atrial receptors are not likely to be responsible for initiating the fall in blood pressure, which is in all probability produced by the activity of ventricular receptors. Moe *et al.* [1944] found that in the dog right atrial injection of veratridine produced a fall in blood pressure 4–12 sec. (average 7 sec. in 8 experiments) after the injection. The blood pressure reached a minimum in 23 sec., and after 74 sec. returned to the level of the control period. If these observations are applicable in the cat, then the view that activity of ventricular receptors produces a reflex fall in blood pressure is strengthened further as the time-course of stimulation of ventricular receptors is similar to the time-course of this reflex. It may be noted here that Daly and Verney [1927] found evidence of left ventricular receptors which produced cardiovascular reflexes. The left atrial receptors must also be concerned in producing reflex vasodepression following these drugs, since it is known that their stimulation leads to a reflex fall in systemic blood pressure [Daly, Ludàny, Todd and Verney, 1937].

Finally, the kind of afferent fibres which Dawes, Mott and Widdicombe [1951] concluded were responsible for the Bezold reflex would seem to correspond in fibre size to the ventricular and atrial fibres described in this paper; *i.e.* these fibres would be blocked round about 10° C., at which temperature the Bezold reflex is blocked in the cat.

The rather large injection-response times, especially in the case of left atrial receptors, suggest that the veriloid alkaloids do not stimulate the cardiac receptors directly, and the possibility that some environmental changes, perhaps ionic, produced by veriloid alkaloids constitute the

mechanism of stimulation has to be borne in mind. It is probably not a case of building up the concentration of alkaloids, because by 48 sec. (mean injection-response time in left atrial fibres) the concentration will have fallen considerably. The studies of Jarisch, Landgren, Neil and Zotterman [1952] on the influence of KCl and sodium citrate are relevant and need to be elaborated further. Jarisch *et al.* [1952] explained the long delay in stimulation of the carotid baroceptors on purely vascular grounds, *i.e.* delay in transportation of the alkaloids to the receptors. To these should now be added the inherent property of veratrum alkaloids in producing a delayed action.

Summary

1. By recording impulses from single afferent units of the cervical vagus of the cat and localizing the receptor with certainty, it has been established that there are receptors in the right and left ventricles which respond to changes in ventricular pressure. These endings are not chemoreceptors.

2. Relatively few ventricular afferent fibres were found. They were characterized by an early systolic burst of impulses, often timed during the isometric phase of ventricular contraction, and in most fibres this burst terminated before mid-systole. Unlike other cardiovascular fibres, fluctuations in impulse activity during normal respiration were infrequent.

3. These ventricular fibres belong to the A group of medullated fibres, and it is estimated that their mean conduction velocity was between 10–20 m/sec.

4. Left atrial fibres with an early systolic burst of impulses as in ventricular fibres were also encountered, but they were rare.

5. All the ventricular receptors and about a third of the left atrial ones (both types A and B) were stimulated by veriloid and veratridine injected into the right atrium. From a consideration of the significant differences in the responses of the ventricular receptors to veriloid and veratridine respectively, and the parallel significant differences in the reflex cardiovascular responses, it was concluded that the ventricular receptors initiate the Bezold reflex.

6. The left atrial receptors contribute to the Bezold reflex but they do not initiate it following veriloid, and are probably chiefly responsible for the prolonged bradycardia of cardiac origin produced by veratridine.

7. The long delay in stimulating the left atrial receptors suggests that the veriloid alkaloids stimulate the receptors secondary to changes either in the alkaloid or in the immediate environment of the receptors.

8. The right atrial receptors (types A and B) were apparently not stimulated by the drugs, and so in the cat they play no part in the Bezold reflex.

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