THE LOCALISATION OF RECEPTORS INVOLVED IN THE REFLEX REGULATION OF THE HEART RATE.

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In 1859 Marey(1) showed that a rise in the arterial blood-pressure was accompanied by a slowing of the heart rate, a fall by a quickening. Since that time numerous investigators have attempted to explain the law of Marey by attributing the change in cardiac rate resultant to change in arterial blood-pressure, either to a central or to a reflex mechanism. That reflex slowing of the heart is brought about by a rise of arterial blood-pressure irrespective of a concomitant change in the cerebral blood-pressure has been conclusively demonstrated by the experiments of Heymans and Ladon(2), Anrep and Segall(3), and Daly and Verney(4). The experiments recorded in this paper were undertaken to localise more exactly the receptors engaged in reflex slowing of the heart.

It has been shown by Eyster and Hooker(5) that mechanical distension of the aorta causes a slowing of the heart in the dog. In their experiments the circulation was abnormal in that the superior and inferior venæ cavæ, the ascending and descending aortæ, and the left subclavian artery were occluded. A rise in venous pressure was shown by Bainbridge(6) to be accompanied by reflex acceleration of the heart, a result which was confirmed by Sassa and Miyasaki(7), who mechanically distended the auricles and large veins by rubber balloons. As far as we have been able to determine, these experimental results of Eyster and Hooker, and Sassa and Miyasaki, are the only ones published which give direct experimental evidence on the localisation of the receptors engaged in reflex changes in cardiac rate.

A. Experimental Results.

Dogs were used in all experiments. Anæsthesia was induced with C and E and fully maintained by an intravenous injection of chloralose, 0·1 grm. per kilo body weight.

I. *Diminished extra-cardiac pressure.* The animals were artificially respired with atmospheric air and the sternum split in order to explore the thoracic viscera. The systemic blood-pressure was taken in the left carotid artery. The pericardium was opened and a Henderson's cardiometer pushed over the ventricles and pressed towards the base of the heart within the pericardium. After tying the free edge of the pericardium around the lip of the cardiometer, the cardiometer itself was fixed rigidly in a clamp, and the outlet tube connected to a mercury or water[1] manometer on the one hand and to a filter pump on the other, for the purpose of recording and of maintaining a negative pressure outside the whole heart. A T-piece fitted with a screw clip was inserted into the tube leading from the pump. This arrangement enabled the negative pressure in the cardiometer to be altered at will.

On lowering the pressure within the cardiometer a slowing of the heart was obtained repeatedly in two experiments. This result was independent of slight changes in blood-pressure in *either* direction (Table I).

TABLE I. Dog. 8·0 kilos. 0·8 grm. chloralose. Cardiometer over whole heart.

	Cardiometer pressure mm. Hg	Heart rate per min.	M.B.P. mm. Hg	
a	0	156	130	
	−2·0	140	120	After 20 secs. duration
	−2·0	140	125	„ 75 „
	0	160	120	
b	0	145	118–125	
	−1·5	126	130	After 5 secs. duration
	−1·5	132	102	„ 15 „
	−1·5	123	112	„ 40 „
	0	135	114	

In a second experiment the subjection of the heart to a negative external pressure of 2 mm. Hg caused immediate cardiac slowing from 144 to 130 beats per minute. This slowing persisted as long as the negative pressure was maintained, viz. 32 seconds, and the release of the pressure was followed by an immediate quickening to 145 beats per minute. The mean arterial blood-pressures in the periods immediately before, during, and immediately after the application of the negative pressure were 101, 99 and 102 mm. Hg respectively, and the right auricular pressures 8·0, 7·8 and 7·9 cm. H_2O respectively.

In the majority of experiments the slowing of the heart was not immediate—there was generally a latent period of from 5 to 25 seconds. The cardiac slowing associated with the negative pressure in the cardio-

[1] All cardiometer pressures have been converted to mm. Hg for convenience of comparison.

meter was dependent upon the integrity of the vagi and was found to be independent of the venous pressure taken in the right auricle.

II. *Diminished extra-ventricular pressure.* In this series of experiments the cardiometer, fitted with a rubber membrane and sleeve, was placed over the ventricles only. A reduction in the pressure surrounding the ventricles was followed by slowing of the heart, the slowing again being dependent on the integrity of the vagi. This phenomenon occurred also in the eviscerated preparation. The suprarenals were removed in addition to the stomach and gut, and the liver securely clamped as near the hepatic veins as was compatible with there being no hindrance to the flow of blood through the inferior vena cava. Gross rises in arterial pressure were avoided by placing T cannulæ in the descending thoracic aorta and the inferior vena cava near its entrance to the right auricle (after partially defibrinating the animal and injecting 0·1 grm. heparin intravenously) and connecting the side limb of one T cannula to that of the other via a variable shunt resistance. Fig. 1 shows the effect of

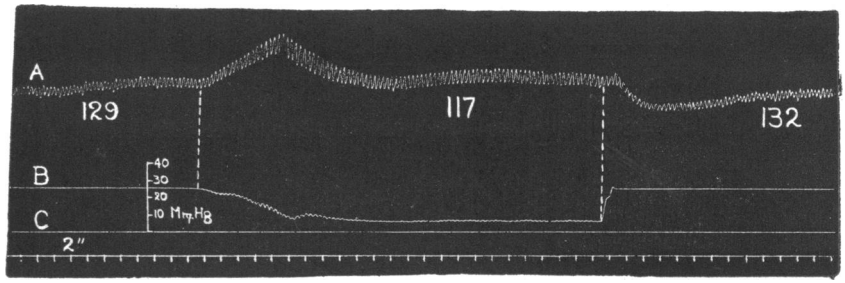

Fig. 1. *A* = arterial pressure. *B* = pressure within cardiometer, mm. Hg, the pressure being zero at beginning and end of tracing. *C* = zero blood-pressure. The heart rate is given immediately below the blood-pressure trace. Vagi intact. Time = 2 secs.

diminishing the extra-ventricular pressure in such a preparation. The temperature in the inferior vena cava was constant at 35·5° throughout. The slowing no longer occurs after cutting the vagi in the neck (Fig. 2).

It was conclusively shown that the presence of the lower portion of the animal was not essential to the manifestation of the reflex cardiac slowing on lowering the extra-ventricular pressure, by sectioning the animal at the level of the eighth thoracic vertebra and connecting the descending aorta via a variable pressure shunt with the inferior vena cava. Fig. 3 is taken from such an experiment: after the vagi were cut the ventricles were again subjected to a negative pressure of 15 mm. Hg

for 28 seconds, and the heart rates before, during and after this subjection were 126, 132 and 132 beats per minute respectively.

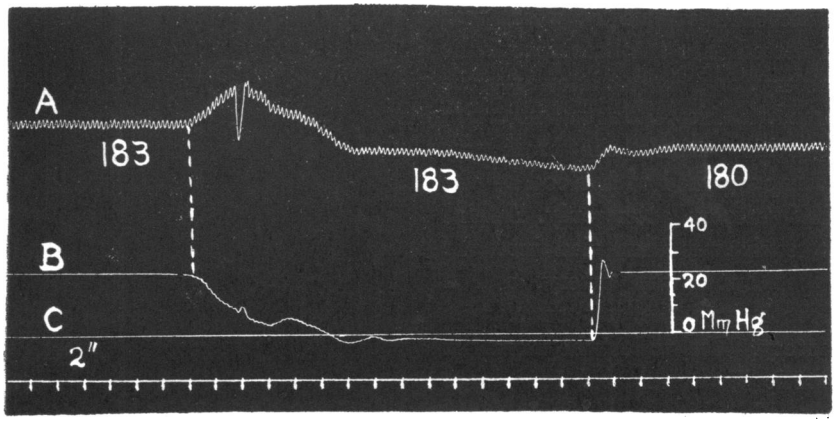

Fig. 2. The letters and figures have the same meaning as in Fig. 1 (*q.v.*). Vagi cut.

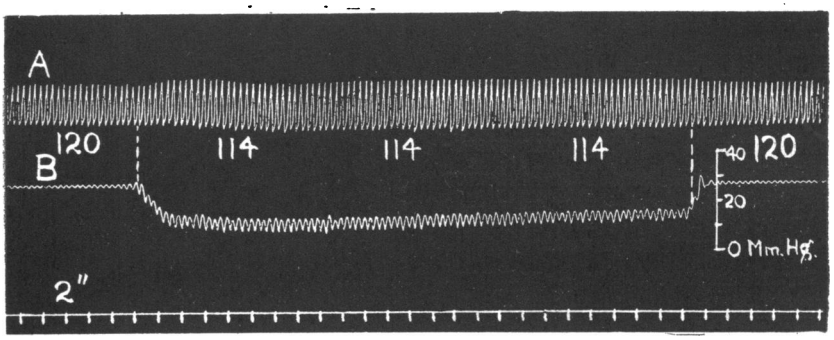

Fig. 3. The letters and figures have the same meaning as in Fig. 1 (*q.v.*). Vagi intact.

III. *Raised intra-ventricular pressure.* In order to produce a rise in left intra-ventricular pressure independently of a concomitant rise in aortic pressure, the following technique was devised. After anæsthetising the animal with C. and E. and chloralose, artificial respiration was commenced and the chest opened. The subclavian arteries were exposed and two ligatures placed loosely around each. The origins of the aorta and brachiocephalic artery were similarly dealt with, and three further ligatures placed loosely round the descending aorta immediately above the diaphragm. A large T cannula (*E*, Fig. 4) was then inserted into the

thoracic aorta and tied firmly in position. This cannula communicated by means of a length of wide bore rubber tubing with a T-piece at *H*, the side limb of which passed to a second cannula *D*, which was inserted into the brachiocephalic artery, and directed towards the head. During the actual insertion of this cannula the brain was being supplied with blood by the left vertebral artery only. A third cannula was then tied into the right subclavian artery, and a fourth into the left subclavian artery. The wide tube from the aortic T cannula led to a large cannula which was inserted into the aorta in such a manner that the edge of the cannula just avoided occluding the origins of the coronary arteries, the aorta itself being ligatured immediately distal to the point of insertion of the cannula. During this manipulation the superior and inferior venæ cavæ were occluded, and released immediately the aortic cannula had been tied in position. The final disposition of the cannulæ and their connections was as shown diagrammatically in Fig. 4, the blood-pressure being recorded from the three sites indicated. In such a preparation, therefore, we are able to record simultaneously the pressures at the aortic orifice (*A*), the cerebral pressure (*B*), and the pressure in the aortic arch (*C*). Further, by impeding the blood flow by compression at the appropriate site, we can vary these pressures independently of each other.

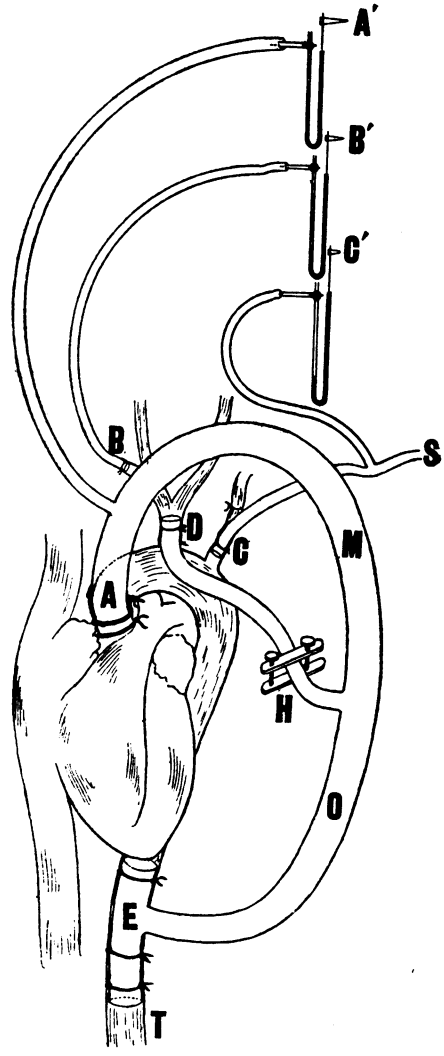

Fig. 4. Diagrammatic representation of the disposition of cannulæ and tubes used in experiments on the effect, on the heart rate, of independent variations in the blood-pressure in the left ventricle, brain and aortic arch.

When the aorta was compressed at *T* a rise in all the three pressures was produced, and this rise was accompanied by cardiac slowing. For example, a rise in pressure at the aortic orifice from 118 to 155 mm. Hg, the cerebral and aortic arch pressures undergoing a parallel change, was accompanied by slowing of the heart rate from 133 to 120 beats per minute. On release of the aorta the rate gradually rose, to reach its original value of 133 after an interval of 30 seconds.

Compression at *O* (Fig. 4) raised the pressure at the aortic orifice from 126 to 192 mm. Hg. The cerebral pressure underwent a parallel change, whilst the aortic arch pressure fell from 100 to 14 mm. Hg, the heart rate falling from 156 to 142 beats per minute. Release of the compression at *O* was accompanied by the return of the three pressures to their original values and a gradual increase in the heart rate to 152 beats per minute. This rate was attained 20 seconds after the release.

By compression at *T* accompanied by adjustment of the screw clip *H* so that the cerebral pressure was maintained constant, a slowing was again encountered. For example, the pressure at the aortic orifice rose in one experiment from 100 to 171 mm. Hg, the aortic arch pressure undergoing a parallel rise, the cerebral pressure, however, being maintained at its original level. The heart rate fell from 150 to 145 immediately, to fall still further to 138 after the pressures *A'* and *C'* (Fig. 4) had been maintained at the high level for 30 seconds. 15 seconds after the compression at *T* was released the pressures had returned to their previous levels and the heart rate was then 160 per minute.

Table II shows the effect of compression at *O* accompanied by compensatory tightening of the screw clip so that the cerebral pressure remained constant. It will be seen that a rise in the pressure at the aortic orifice is accompanied by slowing of the heart in spite of the cerebral pressure remaining approximately constant and of the aortic arch pressure falling.

TABLE II.

Pressure at aortic orifice mm. Hg	Cerebral B.P.	Pressure in aortic arch	Heart rate	
122	108	108	210	
				Compress *O* Compensate at *H*
206	102	78	205	
222	96	55	190	
210	104	62	195	
				Release *O* + *H*
116	105	106	210	

Lastly, compression at *M* produced, as might be expected, a rise in the pressure at the aortic orifice accompanied by a fall in cerebral and

aortic arch pressures. In spite of the fall in these pressures a slowing of the heart was produced. An example of this result is shown in Fig. 5.

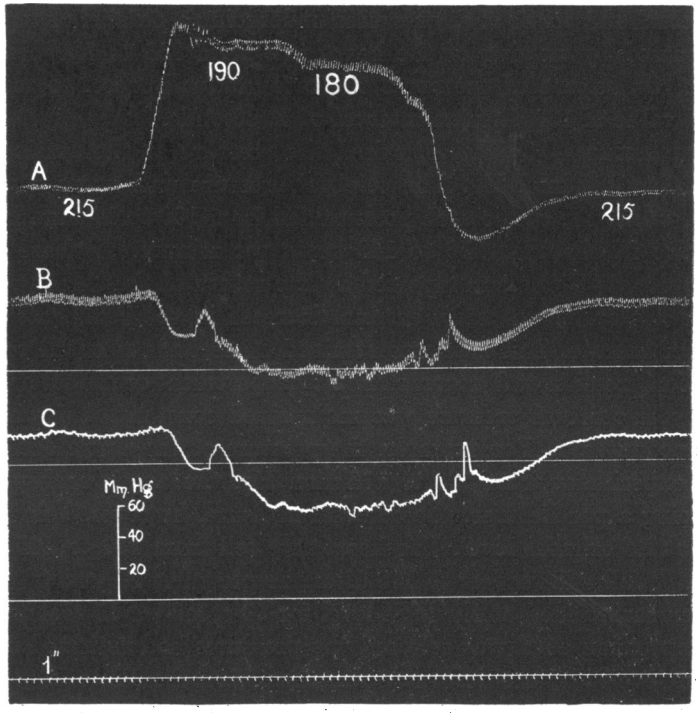

Fig. 5. A = blood-pressure at aortic orifice. B = cerebral blood-pressure. C = blood-pressure in aortic arch. The horizontal lines correspond respectively to the zero levels of the three pressures. The figures below A give the heart rate per minute.

In the experiments illustrated by Table II and Fig. 5 a minimal cut only was made in the pericardium, the cut being just sufficient to allow the aortic ligatures to be placed in position. In the other experiments of this series the pericardium was freely opened.

The position of the aortic cannula was invariably examined post-mortem and it was found that the edge of the cannula was never more than 3 mm. away from the origins of the coronary arteries. Indeed, in some experiments the distance was 1 mm. only (see Fig. 6). The distance from the lip of the cannula to the ligature holding it in position (C, Fig. 6) was 6 mm. The part of the aortic wall central to this ligature, however, rather than that central only to the edge of the cannula, must be considered as being exposed to the changes of pressure registered by the

manometer *A'* (Fig. 4). In these experiments, therefore, we have not decisively excluded the potential participation of the most proximal part

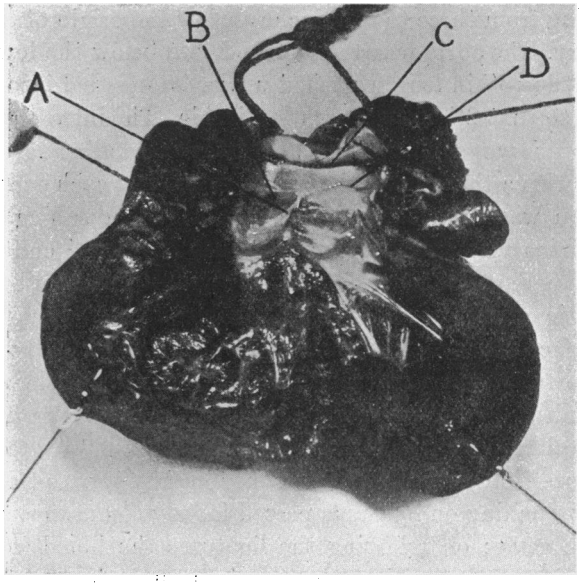

Fig. 6. *A* = aortic orifice. *B* = origin of right coronary artery. *C* = ligature which held aortic cannula in position, showing through the intima. *D* = groove in intima marking the position of the edge of the cannula.

of the aorta in the initiation of the cardio-inhibitory reflex. It is clear, however, that the amount of aortic wall left between the cannula and the ventricle was small, and it seems reasonable to attribute the slowing in rate which accompanied a rise in pressure in the manometer *A'* with constant or lowered pressures in manometers *B'* and *C'* to a rise in the intra-ventricular pressure or coronary arterial pressure or both, rather than to the increased pressure exerted on the remaining fragment of aortic wall.

We may conclude, therefore, from this series of experiments that a rise in left intra-ventricular pressure with a concomitant rise or a fall in aortic pressure, the cerebral pressure remaining constant throughout, or falling, is accompanied by slowing of the heart. The slowing was again found to be dependent on the integrity of the vagi.

IV. *Raised aortic pressure.* After opening the thorax by splitting the sternum 500–700 c.c. of the blood was replaced by defibrinated blood obtained from another dog, and 10 mgm. of heparin per kilo body weight

were then injected intravenously. The arterial blood-pressure was taken in the left carotid artery. Two ligatures were placed round the thoracic aorta about one and a half inches apart, the mid-point between the ligatures being from three to four inches below the origin of the left subclavian artery. The aorta was then opened just below the lower ligature and a brass tube 3″ in length pushed upwards and tied into the lumen of the aorta so that 2″ of its length lay inside. The intra-aortic portion of this brass tube was slightly curved to fit the descending aortic arch and was covered with a thin rubber sleeve tied round it at each end; the extra-aortic portion was connected to a length of rubber tubing fitted with a cannula which was inserted and tied into the distal end of the cut aorta. A fine bore metal tube, piercing the wall of the main brass tube in its extra-aortic course, passed upwards within its lumen and opened on the outer surface in the middle of the intra-aortic portion. By connecting the fine bore tube to a pressure apparatus, the rubber sleeve could be expanded and an internal pressure applied to the walls of the aorta without any alterations in the resistance to the blood flow taking place. During the insertion of the brass tube, the blood supply to the heart was diminished by pulling on ligatures placed loosely round the superior and inferior venæ cavæ; on releasing the ligatures the blood from the descending portion of the aortic arch passed through the brass tube, then through the rubber tube connecting it to the distal part of the descending thoracic aorta. A Cenco blower, with an adjustable pressure valve, supplied the power for the inflation of the rubber sleeve.

Distension of the walls of the aorta by this method was carried out in six experiments. In one experiment the results were negative, in the remaining five slowing of the heart rate occurred without a rise in arterial blood-pressure (Fig. 7). In two of these experiments the cardiac slowing was followed by ventricular fibrillation. Garrey(8) found that vagal stimulation may stop ventricular fibrillation in the dog, an observation which, when taken in conjunction with our own, suggests that the result on the heart of electrical stimulation of the vagi and of vagal stimulation evoked by aortic distension may be entirely different. In two of our experiments it was found that after vagal section aortic distension was without effect on the heart rate. In the remainder vagal section was not resorted to.

B. Discussion.

In this paper we believe we have produced experimental evidence to show that the receptors engaged in reflex cardiac slowing resultant to a

rise in aortic pressure in the dog, are distributed over a considerably wide, area. The experiments described in section IV prove conclusively that some at any rate are situated in the upper portion of the descending thoracic aorta. Others, the presence of which is shown by the experiments recorded in sections I to III, are more difficult to locate precisely, though the evidence points conclusively to their being placed in one or more of

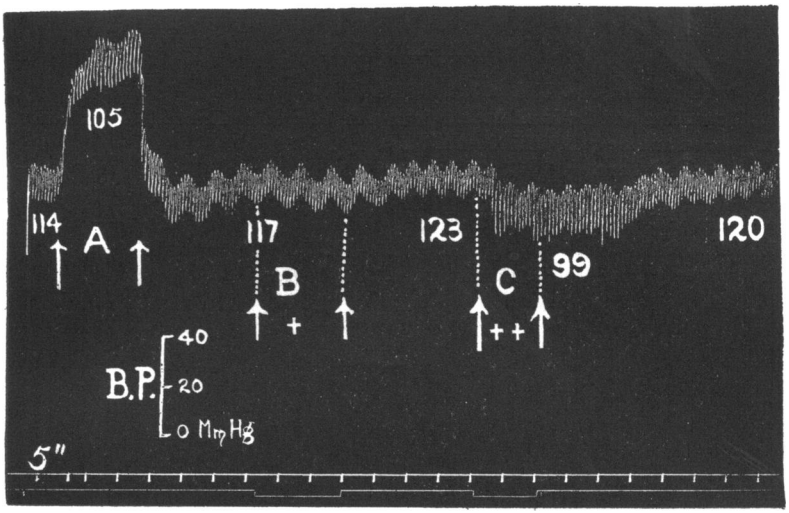

Fig. 7. Between arrows: at *A*, rubber connection between brass tube and distal end of aorta compressed; at *B*, aorta moderately distended; at *C*, aorta heavily distended by inflection of rubber sleeve. Heart rate per minute shown by figures below blood-pressure tracing. Time 5 secs. Bottom signal, duration of aortic distension.

three situations, viz. ventricles, coronary arteries and lungs. Further experiments will be required to differentiate satisfactorily between these various possibilities. The point, however, which we wish to stress as the result of the present series of experiments is that we have been able to demonstrate two separate sites in which the receptors are found, namely, the thoracic aorta on the one hand, and the heart or lungs or both, on the other.

C. Summary.

1. In the dog a negative pressure applied to the whole heart or only to the ventricles causes a reflex slowing of the heart.

2. A rise in intra-ventricular pressure with the aortic pressure kept constant causes reflex slowing of the heart.

3. Distension of the aorta without a rise in aortic arterial pressure causes reflex slowing of the heart.

4. The slowing of the heart (1, 2, 3, above) is dependent on the integrity of the vagi.

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