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GRADATION OF THE REFLEX RESPONSE FROM ATRIAL RECEPTORS

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SUMMARY

1. In anaesthetized dogs, distension of balloons so as to stimulate atrial receptors resulted in a reflex increase in heart rate.

2. Successive distensions of one, two and three balloons positioned in the left upper and middle pulmonary vein–atrial junctions and in the left atrial appendage resulted in a progressive increase in the magnitude of this response.

3. It is concluded that the magnitude of the increase in heart rate is related to the extent of receptor area stimulated.

INTRODUCTION

Stimulation of atrial receptors has been shown to result in a reflex increase in heart rate; the afferent path of this reflex is at least partially in the vagi and the efferent solely in the sympathetic nerves to the heart (see Linden, 1972, for references). However, the investigations so far reported have failed to demonstrate a relationship between the intensity of the stimulus and the magnitude of the response; the present investigation was undertaken to resolve this problem. A preliminary report of this investigation has already been given to the Physiological Society (Kappagoda, Linden & Mary, 1975).

METHODS

Six dogs weighing 18–24 kg were anaesthetized with α-chloralose (0·1 g/kg I.V.) and artificially respired. The techniques for the induction and maintenance of anaesthesia have been described previously (Kappagoda, Linden & Snow, 1972).

The chest was opened through the fifth intercostal space on the left side and small latex balloons were placed in the left atrial appendage and at each of the left upper and middle pulmonary vein–atrial junctions (Ledsome & Linden, 1964; Kappagoda, Linden & Saunders, 1972). The appendage and the pulmonary vein–atrial junctions were stretched by distending the balloons with warm saline, the

appendage with 2·5 ml. (mean; range 2–3·5) and the vein–atrial junctions each with 1·1 ml. (mean; range 1–1·5).

Pressures in the cardiovascular system and in the trachea, the e.c.g. and the end-tidal $\bar{P}_{CO_2}$ were recorded as described previously (Kappagoda, Linden & Snow, 1972). The oesophageal temperature and the acid–base status of the animal were measured and maintained within normal limits.

Bretylium tosylate (Darenthin, Burroughs and Wellcome; dose 10 mg/kg) was given intravenously to block transmission in the sympathetic nerves to the heart.

RESULTS

In five dogs recording commenced approximately 2½ hr after the initial dose of anaesthetic had been given. In the remaining dog recording commenced 7 hr after the initial anaesthetic. In these dogs, the initial heart rate was 89 beats/min (mean; range 48–133) the mean pressure in the femoral artery was 124 mmHg (mean; range 99–150) and the mean pressure in the left atrium was 7·5 cmH_2O (mean; range 5·0–13). The pH, P_{CO_2} and P_{O_2} of arterial blood were 7·36 (mean; range 7·31–7·42), 37 mmHg (mean; range 33–41) and 229 mmHg (mean; range 200–250) respectively. The haematocrit was 37 % (mean; range 34–40).

The atrial receptors were stimulated by distending the balloons located at the vein–atrial junctions and in the appendage. The response of an increase in heart rate by stimulation of atrial receptors was demonstrated by adopting the protocol previously described (Ledsome & Linden, 1964; Kappagoda, Linden & Saunders, 1972). The response was expressed as the difference between the heart rate during the period of distension and the average of the heart rates during the control periods, before and after the period of distension. Records obtained in an experiment when all three balloons were distended simultaneously are shown in Fig. 1. The heart rate before distension was 94 beats/min, was 162 beats/min during distension, and after distension, in the final control period, was 116 beats/min; thus the response was an increase in heart rate of 57 beats/min.

In each dog the successive responses produced by the distension of balloons in the following sequence were determined: (*a*) left upper pulmonary vein–atrial junction alone; (*b*) left upper and middle pulmonary vein–atrial junctions; (*c*) both vein–atrial junctions and the left atrial appendage; and finally (*d*), again the left upper pulmonary vein–atrial junction alone. This sequence of distensions was performed twice in five dogs. An example of the responses obtained from one dog is illustrated diagrammatically in Fig. 2. The response produced by the first distension of the balloon at the left upper pulmonary vein–atrial junction alone was an increase in heart rate of 15 beats/min. Distension of two and three balloons resulted in increases in heart rate of 26 and 51 beats/min respectively. A second distension of the balloon at the left upper pulmonary

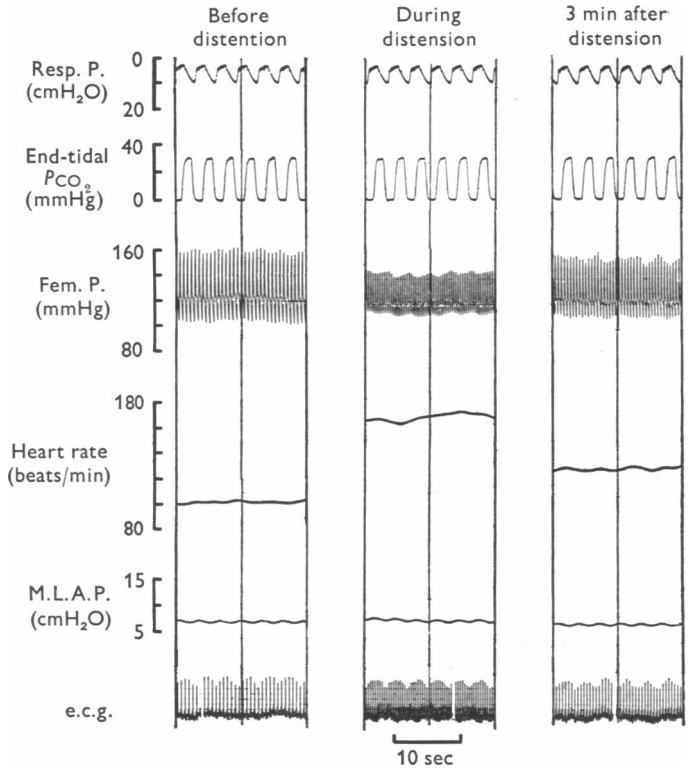

Fig. 1. Effect of stretching the left upper and middle pulmonary vein–atrial junctions and the left atrial appendage (three balloons). Dog no. 7. From above downwards, tracheal pressure (cmH_2O), end-tidal P_{CO_2} (mmHg), femoral arterial pressure (mmHg), heart-rate (beat/min), mean left atrial pressure (cmH_2O) and the electrocardiogram. Records obtained immediately before distension of the balloons (heart rate, 94 beats/min), during distension (heart rate 162 beats/min) and 3 min after distension (heart rate 116 beats/min). Mean increase in heart rate 57 beats/min.

vein–atrial junction to complete the first sequence of distension resulted in an increase in heart rate of 12 beats/min. The second sequence of distensions also resulted in responses which were similar to the first.

The results from the other five dogs were qualitatively similar to those shown in Fig. 2. In any one dog, the responses produced by distension of one balloon alone (left upper pulmonary vein–atrial junction) was the smallest and those produced by distension of all three balloons (both vein–atrial junctions and the appendage) were the largest. The balloon at the left upper pulmonary vein–atrial junction was distended a total of twenty-four times to produce a mean increase in heart rate of 10·8 beats/min. The balloons at the left upper and middle pulmonary vein–

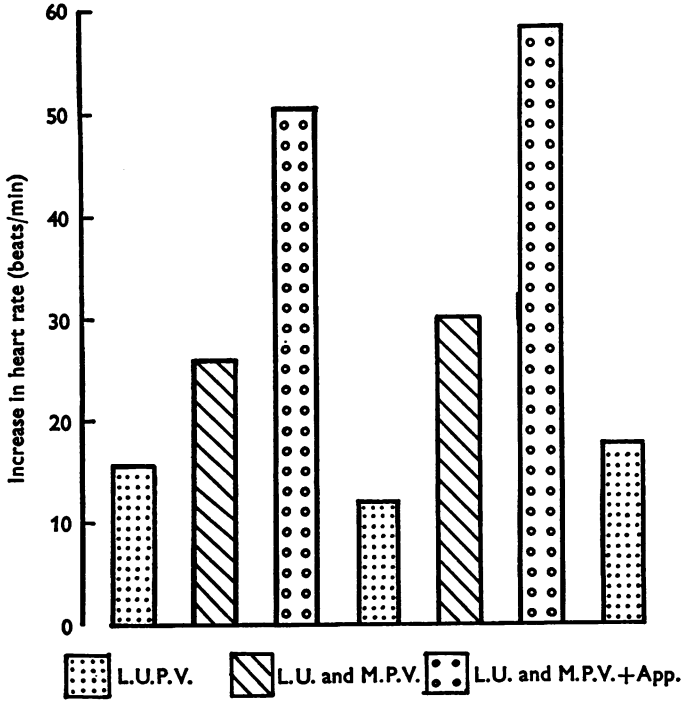

Fig. 2. Gradation of the responses to distension of the balloons (dog no. 7). L.U.P.V., distension of the balloon in left upper pulmonary vein alone; L.U. and M.P.V., distension of the two balloons in left upper and middle pulmonary veins respectively; L.U. and M.P.V.+App., distension of the three balloons in the left upper and middle pulmonary veins and in the left atrial appendage respectively. The responses are expressed as increases in heart rate (beats/min).

atrial junctions were distended twelve-times to yield a mean increase in heart rate of 22·2 beats/min. The balloons at both vein–atrial junctions and in the atrial appendage were distended ten times, which produced a mean increase in heart rate of 35·2 beats/min. Details of the results which demonstrate that the responses are significantly different from each other (two-tailed T test) are presented in Table 1.

In order to confirm the reflex nature of these responses, at the conclusion of five of the experiments the three balloons were distended after the intravenous injection of bretylium tosylate. The response was abolished completely in two dogs and was reduced to 2 beats/min (mean; range 1–3) in the remaining three dogs.

TABLE 1. The gradation of the responses resulting from distension of the balloons (increase in heart rate, beats/min)

	One balloon (left upper pulmonary vein)	Two balloons (left upper and middle pulmonary vein)	Three balloons (left upper and middle pulmonary vein and appendage)
Mean increase in heart rate	10·8	22·2	35·2
Number of distensions	24	12	10
P		$< 0{\cdot}001$	$< 0{\cdot}005$

Changes in pressure in the cardiovascular system

Small changes in the pressures in the femoral artery and in the left atrium were observed. The mean pressure in the femoral artery during the control period was 123·2 mmHg (mean; range 88·5–161) and that during the period of distension was 122·6 mmHg (mean; range 87–157). This difference is not statistically significant ($P > 0{\cdot}5$, two-tailed paired T test). The mean pressure in the left atrium during the control period was 7·6 cmH_2O (mean; range 4·0–12·5) and that during the test was 7·3 cmH_2O (mean; range 4·0–13·0). This difference is statistically significant ($P < 0{\cdot}01$; two-tailed paired T test) but is likely to be the result of the increase in heart rate. There was no correlation between the changes in heart rate and the changes in mean pressure in the left atrium ($R = 0{\cdot}27$; $P > 0{\cdot}05$).

DISCUSSION

Stretching the right and left vein–atrial junctions or the atrial appendages in the anaesthetized dog has been shown to result in a reflex increase in heart rate. It has been shown that the most likely receptors to be involved in this reflex are the atrial receptors. The afferent path of the reflex lies at least partially in the vagi and the efferent solely in the sympathetic nerves to the heart (see Linden (1972) for references). However, the investigations reported so far have failed to demonstrate a correlation between the magnitude of the stretch and the increase in heart rate. It has been suggested that this reflex mechanism is just a 'trigger' response such that once threshold to the receptors is reached the response mounts so rapidly that in effect this reflex could not contribute very much to the every day control of the circulation.

In any reflex response, it should be possible to increase the magnitude of the response by increasing the intensity of the stimulus: (*a*) to recruit a greater number of receptors; (*b*) to increase the frequency of discharge in a group of receptors already excited or; (*c*) to obtain a combination

of the two. In the case of the atrial receptors, it has not been possible to show a consistent increase in the magnitude of the response by attempting to increase the intensity of the stimulus at any one site, i.e. by increasing the volume of saline injected into a balloon (Ledsome & Linden, 1964). It is likely that the peculiar geometrical arrangement of the vein–atrial junctions contributed to this difficulty. The region has the appearance of a truncated cone which is in communication with a spherical cavity and a progressive increment in the distending volume results in the balloon being 'drawn into' lumen of the atrium. Thus the relationship between a given group of receptors and the balloon generating the stretching force is not constant. The present study approached the problem by attempting to recruit successively greater numbers of receptors by sequentially stretching three separate areas, two pulmonary vein–atrial junctions and an appendage.

It has been known since Nonidez (1937) that atrial receptors lie mainly at the vein–atrial junctions. It has been stated (Miller & Kasahara, 1964; Johnston, 1968) that there were no non-encapsulated endings (atrial receptors) in the atrial appendages of dog and man but recently Floyd, Linden & Saunders (1972) demonstrated histologically about ten atrial receptors per atrial appendage in the dog. In addition a reflex increase in heart rate in all respects similar to that evoked by distension of the pulmonary vein–atrial junctions was obtained by distension of the atrial appendages (Kappagoda, Linden & Saunders, 1972). Thus there is both a histological and physiological basis for stretching the atrial appendage so as to stimulate atrial receptors, as in the present investigation.

In the event the present investigation has clearly demonstrated that distension of successive areas containing atrial receptors has resulted in successive increases in the response. Distension of one, two and three balloons resulted in mean increases in heart rate which were significantly different from each other. These responses were unrelated to the changes in pressures in the cardiovascular system and were abolished by the administration of bretylium tosylate which blocks transmission in the sympathetic nerves to the heart. Thus, the responses are qualitatively similar to that demonstrated previously (Ledsome & Linden, 1964). The results support the hypothesis that the response of an increase in heart rate brought about by the stimulation of atrial receptors is related to the number of receptors simulated.

These results also serve to resolve another point of controversy, regarding this reflex. It has been suggested (Paintal, 1973) that the physiological importance of the reflex was limited because the responses reported previously were of a relatively small magnitude (average increase

25 beats/min; see Linden, 1972). The present investigation has clearly established that the magnitude of the response is related to the receptor area stimulated. But the area stimulated by these balloons is small compared to the total area of subendocardial tissue in which the atrial receptors are to be found, e.g. the right atrial receptors at the vein–atrial junctions and in the appendage, the atrial receptors in the right side of the left atrium and an unknown number on the left side of the left atrium would not be stimulated in this investigation. The effect of stimulating all the receptors simultaneously is unknown but if it is assumed that the response may be doubled then this reflex may be important in the control of the circulation.

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