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THE ROLE OF
LEFT ATRIAL RECEPTORS IN THE DIURETIC RESPONSE
TO LEFT ATRIAL DISTENSION

By J. R. LEDSOME and R. J. LINDEN

*From the Cardiovascular Unit, Department of Physiology,
School of Medicine, University of Leeds*

SUMMARY

1. The diuretic response to distension of the whole left atrium caused by obstruction of the mitral orifice has been compared with the effects of distension (by means of small balloons) of the left pulmonary vein/left atrial junctions.

2. Distension of the pulmonary vein/atrial junctions caused an increase in heart rate and a diuresis similar to but smaller than that caused by mitral obstruction.

3. Section of both ansae subclaviae prevented the increase in heart rate produced by distension of the pulmonary vein/left atrial junctions but had little effect on the diuretic response either to pulmonary vein distension or to mitral obstruction.

4. A diuretic response to mitral obstruction could be demonstrated after all nerves from the lungs had been cut but not after the vagus nerves had been cut at levels likely to interrupt the majority of afferent fibres from left atrial receptors.

5. The results support the view that stimulation of left atrial receptors is a major factor in the production of a diuretic response to mitral obstruction.

INTRODUCTION

Partial obstruction of the mitral orifice causes an increase in urine flow in anaesthetized (Henry, Gauer & Reeves, 1956) and unanaesthetized dogs (Lydtin & Hamilton, 1964), but the mechanisms by which the diuresis is produced have not been satisfactorily explained (Ledsome, Linden & O'Connor, 1961). It has been suggested (Henry & Pearce, 1956) that the afferent mechanism involves left atrial distension and stimulation of receptors in the left atrium. The majority of these receptors are situated in the sub-endocardial tissue at the junctions of the pulmonary veins and the left atrium (Coleridge, Hemingway, Holmes & Linden, 1957).

Recently it has been shown that when the pulmonary vein/left atrial junctions are distended by means of small balloons the atrial receptors are strongly stimulated (Kidd, Ledsome & Linden, 1966) and there is a reflex increase in heart rate (Ledsome & Linden, 1964, 1967). The afferent limb of this reflex is in the vagus nerves and the efferent limb is solely in the cardiac sympathetic nerves.

The present investigation was carried out to determine whether distension of the pulmonary vein/atrial junctions could cause diuresis and thus provide further information about the afferent mechanism by which left atrial distension causes diuresis.

METHODS

Dogs of 12–26 kg were given a subcutaneous injection of morphine sulphate (0·5 mg/kg). One hour later under local anaesthesia (decicain 2 %) a catheter was inserted through a saphenous vein into the inferior vena cava and each animal was anaesthetized by an intravenous infusion of a solution of chloralose (British Drug Houses): dose 10 ml. = 0·1 g/kg body wt. in sodium chloride solution (0·6 g/100 ml.). Subsequently during the experimental procedures a steady state of light anaesthesia and fluid input was maintained by the infusion every 10 min of 1·5 ml./kg body wt. of either sodium chloride solution (0·6 g/100 ml.) or the chloralose solution. As soon as possible after the induction of anaesthesia artificial respiration was started with a mixture of 40 % oxygen in air, humidified at room temperature and supplied from a Starling 'Ideal' pump, the rate (about 18/min) and stroke (about 50 ml./3 kg body wt.) of which were adjusted approximately to equal that of the animal's spontaneous respiration. When the chest was opened a resistance to expiration was provided by placing the expiratory outlet from the respiratory pump under 2–3 cm of water.

At intervals during the procedures samples of arterial blood were taken and pH, P_{CO_2}, P_{O_2} and total carbon dioxide content measured; the methods used have been described previously (Norman, Ledsome & Linden, 1965). Appropriate adjustments were made to the respiratory pump or small infusions (10–15 m-equiv) of sodium bicarbonate solution (1 M) were given to maintain P_{CO_2} between 35 and 40 mm Hg and pH within the range 7·3–7·4; no adjustments were made during the control and experimental periods.

The left side of the chest was opened in the fifth intercostal space and a small balloon placed in each of three pulmonary veins (Ledsome & Linden, 1964). In ten experiments a larger balloon was also inserted into the left atrium through the appendage (Ledsome *et al.* 1961).

Femoral arterial pressure was recorded through a metal cannula (Inconel; Johnson, Matthey & Co., London: 1·5 mm bore) and mean left atrial pressure through a 15 cm length of nylon tubing (Portex Plastics, No. 4 surgical nylon). To each cannula was attached a Statham Strain gauge (Model P 23 Gb) and after amplification by means of a carrier amplifier (S. E. Laboratories, Feltham, Middlesex) the pressure was recorded on an ultra-violet light recorder (S. E. Laboratories). The frequency response of the system recording femoral arterial pressure obtained by the method of Linden (1959) was flat (± 5 %) to better than 60 c/s. Mean pressure was obtained electrically by passing the amplifier output through an RC network.

In three experiments the right side of the chest was opened in the fourth intercostal space and a fine stainless-steel wire placed around the right vagus nerve immediately above the root of the right lung and around both roots of the right ansa subclavia. Similar wires were also placed around the left vagus nerve at the level of the upper border of the aorta and

around both roots of the left ansa subclavia. These nerves could then be cut without disturbing the animal by drawing the looped wire through a metal tube (1·5 mm bore) the end of which had been sharpened.

In two experiments the vagus nerves were cooled; the right vagus nerve in the neck and the left vagus nerve at the level of the upper border of the aorta were each placed on a silver-plated copper block which was maintained at 5° C by means of a thermo-electric cooling module (De La Rue Frigistor Ltd., Berks.)

In three dogs a soft polyethylene catheter was placed with the tip in the posterior part of the pericardial cavity overlying the pulmonary veins; the pericardium was then sutured and closed around the catheter. A solution of decicain 2 % was injected through this catheter at an appropriate time to block conduction in nerve fibres in this area.

During the surgical procedures, about 2 hr, the animals received a slow infusion of dextran ('Dextraven', Benger Laboratories Ltd., or 'Dextran 150 in 6 % dextrose', Fisons) of approximately 10 % of their estimated blood volume (100 ml. dextran for 13 kg body wt.). The electrocardiogram was recorded from leads on the forelegs and chest wall; records were taken every 10 min and heart rates were counted from the electrocardiogram over periods of at least 30 sec. Rectal temperature was maintained at 38° C ($\pm$1·5° C) by adjusting heating lamps above and beneath the animal.

Each ureter was catheterized through a flank incision and urine volume measured every 10 min. Urine was analysed for sodium, using a sodium electrode (Electronic Instruments Ltd., BH 104 glass). The electrode was calibrated with gravimetrically prepared sodium chloride solutions covering the range 10–200 mM. The results obtained by this method for urinary sodium are slightly lower than those obtained by the flame photometer (Moore & Wilson, 1963). However, changes in urinary sodium concentration are reliably indicated by the electrode.

RESULTS

Distension of the pulmonary vein/atrial junctions. The left pulmonary vein/left atrial junctions were distended by means of small balloons in ten dogs. Each balloon was distended with 1 ml. saline and the distension was maintained for 30 min; fourteen distensions were made in the ten dogs. In every experiment the heart rate increased within 1–2 min of distending the balloons and decreased over 1–5 min after the distension was ended. Although there were variations in the heart rate over the 90 min of each experimental period, this general pattern was always seen. The average of the heart rates over the 30 min before distension of the balloons was 117 beats/min, increased to an average of 157 beats/min over the 30 min for which the balloons were distended, and decreased to an average of 135 beats/min for the 30 min after deflation of the balloons. Thus the average change in heart rate was an increase of 21 beats/min. The magnitude of this increase in heart rate and the characteristics of the onset and decline of the heart rate changes were similar to those previously described for a series of shorter (3 min) distensions (Ledsome & Linden, 1964). There were no significant changes in mean arterial pressure during the distensions. During the fourteen tests there were only small changes in urine flow (Fig. 1) and in only one experiment was there an increase in urine flow during the experimental period to more than twice the flow during the

control periods. The average change in urine flow was from 0·24 ml./min in the control periods (30 min before balloon distension and the 30 min after the expected diuresis) to 0·29 ml./min during the expected diuresis (the second 20 min of balloon distension and the first 10 min after distension).

A further six balloon distensions were made in five dogs in which both ansae subclaviae had been cut (Fig. 1). Three of these dogs had been previously tested with the ansae subclaviae intact; in the other two dogs
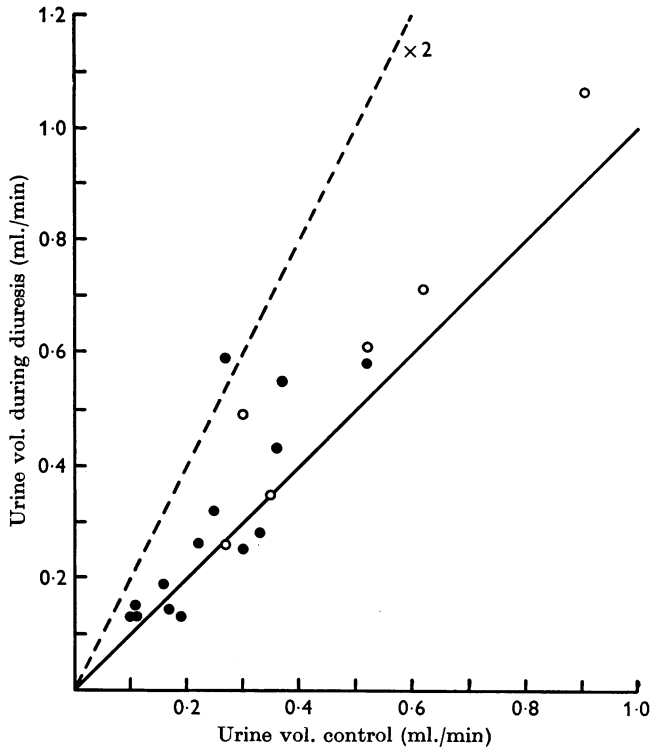

Fig. 1. Effects of distension of the pulmonary vein/atrial junctions. Urine volume during the period of the expected diuretic response compared with urine volume during the control periods (see text). Filled circles, fourteen tests in ten dogs; open circles, six tests in five dogs after cutting both ansae subclaviae. Continuous line is a line of no change. Increases of urine volume to twice the control value would fall on the dotted line.

the ansae subclaviae were cut at the beginning of the experiment. Cutting the ansae subclaviae prevented the increase in heart rate induced by pulmonary vein distension; the average heart rate before distension was 105 beats/min, 112 beats/min during distension, and 113 beats/min after distension. Thus the average change in heart rate was an increase of 3 beats/min. During each of the six tests there were only

small changes in urine flow but these were similar to those seen in the previous group (Fig. 1). The average change in urine flow was from 0·5 ml./min during the control periods to 0·59 ml./min during the experimental periods. On occasions when there were small increases in urine flow the urinary sodium concentration decreased so that sodium excretion remained relatively constant.
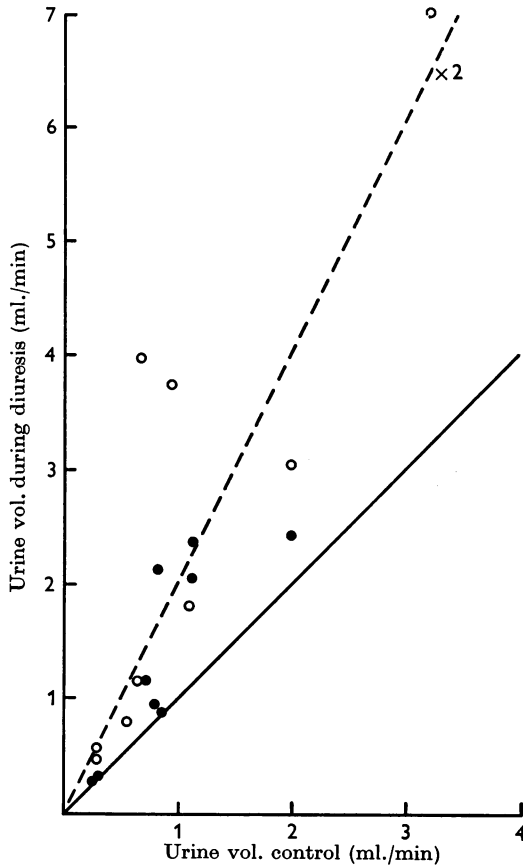

Fig. 2. Urine volume during the period of the expected diuretic response compared with urine volume during the control periods. Open circles, nine tests in five dogs of the effects of mitral obstruction; filled circles, nine tests in the same five dogs of the effect of distension of the pulmonary vein/atrial junctions.

Comparison of the effects of distension of the pulmonary vein/atrial junctions and mitral obstruction. The distension of the small balloons in the pulmonary vein/atrial junctions had resulted in only small changes in urine flow in most of the preparations. Distension of the large balloon which blocked the mitral orifice was known to cause greater responses (Ledsome *et al.* 1961). Because of the protean nature of this response and to eliminate the doubt

that the animals in which the pulmonary/vein atrial junctions had been distended were less 'responsive', the two methods of stimulation were compared in the same animals. Seven animals were prepared in which small balloons were inserted into the pulmonary vein/atrial junctions and in which a large balloon was placed in the left atrium. Tests were made alternately of the effects of distending the balloons in the pulmonary vein/ atrial junctions for 30 min and of inflating the large balloon for 30 min. The large balloon was distended with saline (about 1 ml./kg body wt.) until it caused obstruction of the mitral orifice such that there was a rise in left atrial pressure of about 20 cm H_2O as described previously (Ledsome *et al.* 1961). A period of at least 90 min was allowed between the end of one test and the beginning of the next. Two experiments were abandoned, one when the dog died after the large balloon had burst, a second in which the dog had a very low urine flow, less than 0·1 ml./min, and showed no diuretic response to mitral obstruction.

The results from five dogs are therefore described. In two dogs mitral obstruction was tested first, in the other three dogs the pulmonary vein balloons were distended first. A total of nine tests of mitral obstruction and nine tests of pulmonary vein distension was made in the five dogs. The changes in urine flow which occurred are shown in Fig. 2. Distension of the small balloons in the pulmonary veins caused a small increase in urine flow in five of the nine tests, whereas mitral obstruction caused an increase in urine flow in all nine tests. The two groups of tests are further compared in Fig. 3, which shows the averaged values of the measured parameters during the control and experimental periods in all eighteen tests. Thus, whereas distension of the pulmonary veins caused an average increase in urine flow to 1·5 times the control flow, mitral obstruction in the same dogs caused an average increase to 2·7 times the control flow The time course of the changes was similar in the two groups of tests and there were only small changes in sodium excretion in both groups. The large increase in urine flow during mitral obstruction occurred in spite of a fall (5 mm Hg) in mean arterial pressure.

Because in these experiments there is often great variation in the responses of individual dogs and even in the same dog from time to time, quantitation of the response is always difficult and differences occurring in one dog are often more convincing than those for a group. The complete data for one experiment are therefore plotted in Fig. 4. In this experiment distension of the pulmonary vein/atrial junctions by means of small balloons caused an increase in heart rate and a small diuresis during each of two tests. However, mitral obstruction, although accompanied by a small (5 mm Hg) fall in mean arterial pressure, was associated with a very much larger diuretic response. Thus it may be concluded that distension

of the pulmonary vein/atrial junctions may produce a small diuresis with characteristics similar to those induced by mitral obstruction but that mitral obstruction provides a more effective stimulus.

Mitral obstruction and nerve section. In three dogs the effects of mitral obstruction for periods of 30 min caused by distension of a balloon in the left atrium were tested. Both ansae subclaviae were then cut and in the three dogs the test of mitral obstruction was repeated. Finally, the left
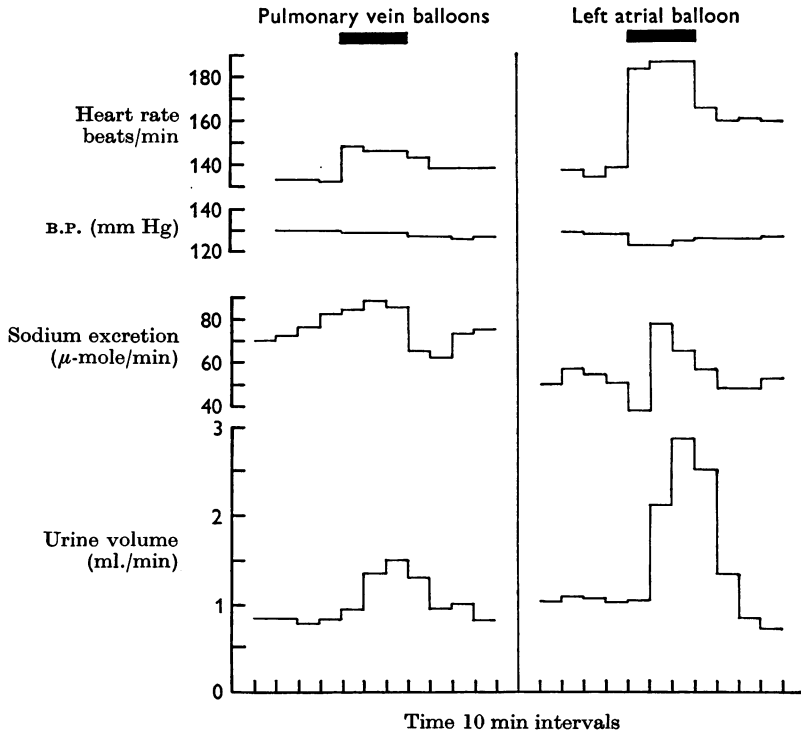

Fig. 3. Changes in heart rate, mean arterial pressure, sodium excretion and urine volume produced by distension of the pulmonary vein/atrial junctions and by mitral obstruction caused by inflating a balloon in the left atrium. Each horizontal line is the average of nine individual values from five dogs.

vagus nerve was cut at the level of the upper border of the aorta and the right vagus nerve was cut just above the lung root and the test of mitral obstruction repeated in all three dogs. One such experiment is shown in Fig. 5. Each period of mitral obstruction was accompanied by an increase in urine flow; at the same time the urine became more dilute. Although the absolute size of the diuresis was reduced in successive tests it should be noted that the urine flow during the control periods was also gradually falling so that the size of each diuresis relative to its control periods changed

considerably less. Also the first test in this dog produced the largest diuresis yet seen and the diuresis was followed by an increased sodium excretion lasting for about 1 hr. Two other dogs which also produced a large diuresis each showed similar increases in sodium excretion. This change may have
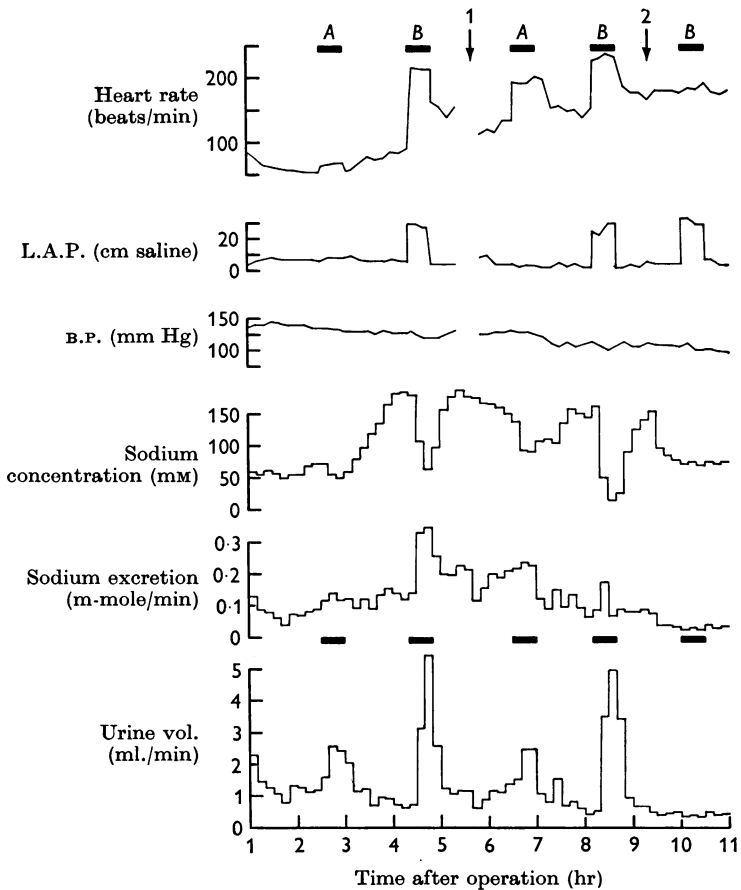
Fig. 4. Change occurring in measured variables during one experiment. During *A* small balloons were distended in the pulmonary vein/atrial junctions. During *B* a balloon was distended in the left atrium to cause mitral obstruction. There is a break in the record at ' 1 ', when the atrial balloon was replaced because it leaked. At ' 2 ' the right vagus nerve was cut in the neck and the left vagus nerve was cut at the level of the upper border of the aorta.

been associated with the large diureses produced in these animals, as it was not apparent in the previous investigation (Ledsome *et al.* 1961). The changes in urine flow in the three dogs are shown in Table 1 (Expts. 53, 55, 56). The average increase in urine flow caused by mitral obstruction with all nerves intact was 220 %; with both ansae subclaviae cut the average

increase during the diuresis was 140 % and with the vagus nerves cut as described urine flow increased by 65 %. The increases in urine flow which occurred in these three dogs with nerves intact were exceptionally large, and it should be noted that the increases which occurred in these dogs with the ansae subclaviae cut were still larger than for the average of the eight dogs with intact nerves in Table 1. The increase in heart rate caused by mitral obstruction was reduced after cutting both ansae subclaviae (Fig. 5). Where the nerves were intact the average heart rate in the three dogs during the control periods was 105 beats/min and increased to 172 beats/min during mitral obstruction; after cutting the ansae subclaviae heart rate increased from 109 beats/min to 137 beats/min during mitral obstruction.
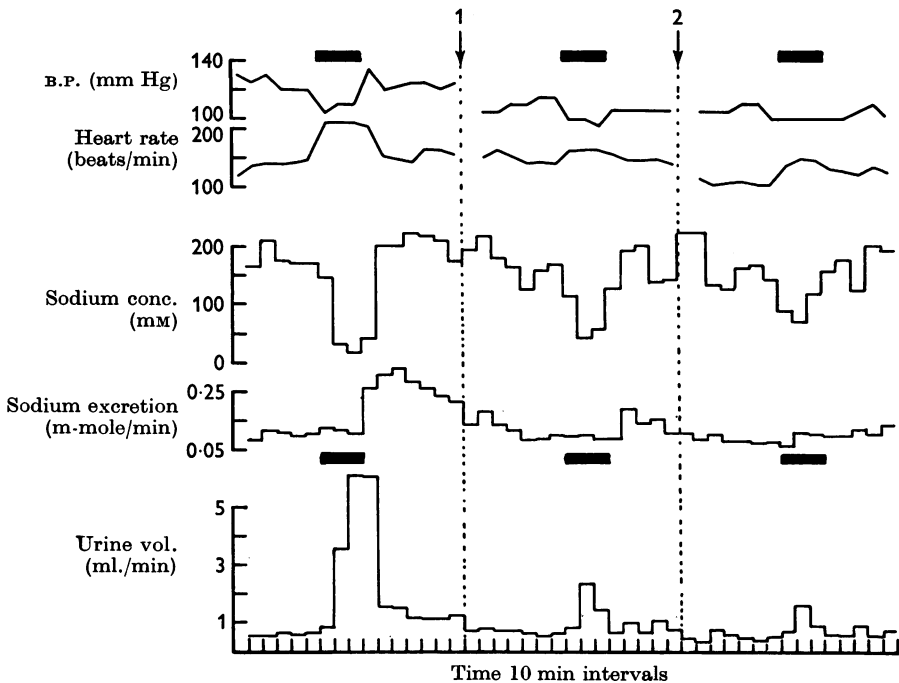

Fig. 5. Effects of left atrial distension before and after nerve section. Horizontal bars represent periods during which a balloon was inflated in the left atrium to cause mitral obstruction. At '1' both ansae subclaviae were cut; at '2' the right vagus nerve was cut immediately above the lung root and the left vagus nerve was cut at the level of the upper border of the aorta.

In four other dogs which had been shown to produce a diuretic response to mitral obstruction the right vagus nerve in the neck was cut or cooled to 6° C and the left vagus nerve at the upper border of the aorta was cut or cooled to 6° C. Mitral obstruction performed with the vagus nerves blocked at these sites was always accompanied by *a decrease* in urine flow

TABLE 1. Changes in urine volume during distension of a balloon in the left atrium before and after section or cold block of nerves. Numbers are average values, A for 30 min before balloon distension, B during last 20 min of balloon distension and the first 10 min after balloon distension, C the 30 min following B, % = percentage change in urine volume

Urine volume (ml./min)

Expt. no.	Nerves intact				Both ansae subclaviae cut				Vagi cut. Left, at upper border of aorta — R. above lung root				R. in neck			
	A	B	C	%	A	B	C	%	A	B	C	%	A	B	C	%
53 (1)	1·89	3·40	1·95	+76	—	—	—	—	—	—	—	—	—	—	—	—
(2)	—	—	—	—	0·69	2·03	0·62	+210	—	—	—	—	—	—	—	—
(3)	—	—	—	—	—	—	—	—	0·38	0·83	0·50	+89	—	—	—	—
55 (1)	0·59	5·26	1·34	+440	—	—	—	—	—	—	—	—	—	—	—	—
(2)	—	—	—	—	0·62	1·52	0·86	+105	—	—	—	—	—	—	—	—
(3)	—	—	—	—	—	—	—	—	0·49	1·02	0·61	+85	—	—	—	—
56 (1)	1·46	2·89	0·86	+150	—	—	—	—	—	—	—	—	—	—	—	—
(2)	—	—	—	—	0·95	1·55	0·44	+110	—	—	—	—	—	—	—	—
(3)	—	—	—	—	—	—	—	—	0·41	0·46	0·44	+10	—	—	—	—
57 (1)	2·54	3·75	1·27	+97	—	—	—	—	—	—	—	—	—	—	—	—
(2)	—	—	—	—	—	—	—	—	0·43	0·77	0·40	+83	—	—	—	—
23 (1)	0·34	1·95	0·33	+480	—	—	—	—	—	—	—	—	—	—	—	—
(2)	—	—	—	—	—	—	—	—	—	—	—	—	0·48	0·38	0·45	−18
25 (1)	0·57	3·03	2·89	+75	—	—	—	—	—	—	—	—	—	—	—	—
(2)	—	—	—	—	—	—	—	—	—	—	—	—	0·54	0·13	0·38	−72
80 (1)	0·49	1·75	1·27	+100	—	—	—	—	—	—	—	—	—	—	—	—
(2)*	—	—	—	—	—	—	—	—	—	—	—	—	0·44	0·30	0·24	−12
(3)	0·47	1·18	0·45	+160	—	—	—	—	—	—	—	—	—	—	—	—
81 (1)	1·08	2·95	2·19	+81	—	—	—	—	—	—	—	—	—	—	—	—
(2)*	—	—	—	—	—	—	—	—	—	—	—	—	1·39	0·88	2·05	−49
(3)	1·37	2·02	1·10	+64	—	—	—	—	—	—	—	—	—	—	—	—
Average	1·08	2·81	1·36	+130	0·75	1·70	0·64	+141	0·43	0·77	0·49	+67	0·71	0·42	0·78	−43

* Vagi cooled to 6° C (thermode to 5° C).

(Figs. 4, 6). There was also a decrease in sodium excretion during mitral obstruction with the vagus nerves cooled. The diuretic response returned when the nerves were rewarmed (Fig. 6).

In three dogs the effect of mitral obstruction was tested before and after injecting 2 ml. decicain into the pericardial sac. In two dogs a diuretic response to mitral obstruction was obtained during the period before injection of decicain and about $2\frac{1}{2}$ hr later after the pericardial sac had
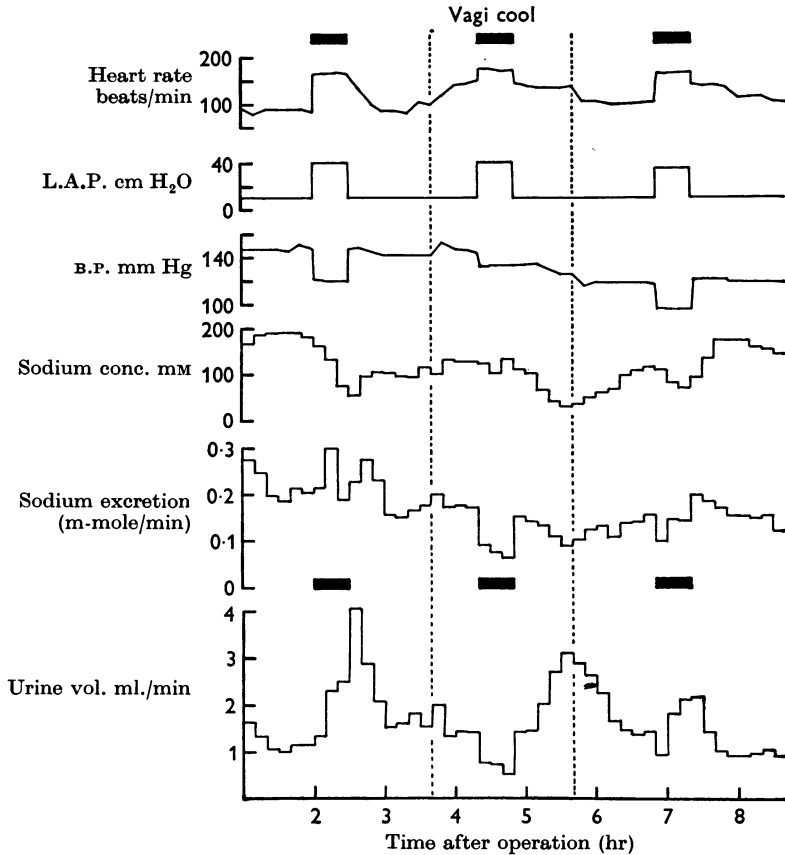

Fig. 6. Effects of left atrial distension before, during and after cooling the vagus nerves. A balloon was inflated in the left atrium to cause mitral obstruction during the periods indicated by the horizontal bars. Between the broken lines both vagus nerves were cooled to 6° C (thermode to 5° C): the right vagus nerve in the neck and the left vagus nerve at the level of the upper border of the aorta.

been washed out with saline and the effects of the decicain had worn off. Distension of the balloon in the left atrium during the experimental period 40 min after injection of the decicain caused a decrease in urine flow and sodium excretion in these two dogs. An example of one experiment is shown

(Fig. 7). In the third dog, although decicain abolished the response, the response did not return after washing out the pericardial sac. Examination at the end of the experiment showed the methylene blue which had been mixed with the decicain solution to be concentrated mainly around the intrapericardial portions of the pulmonary veins. However, there was
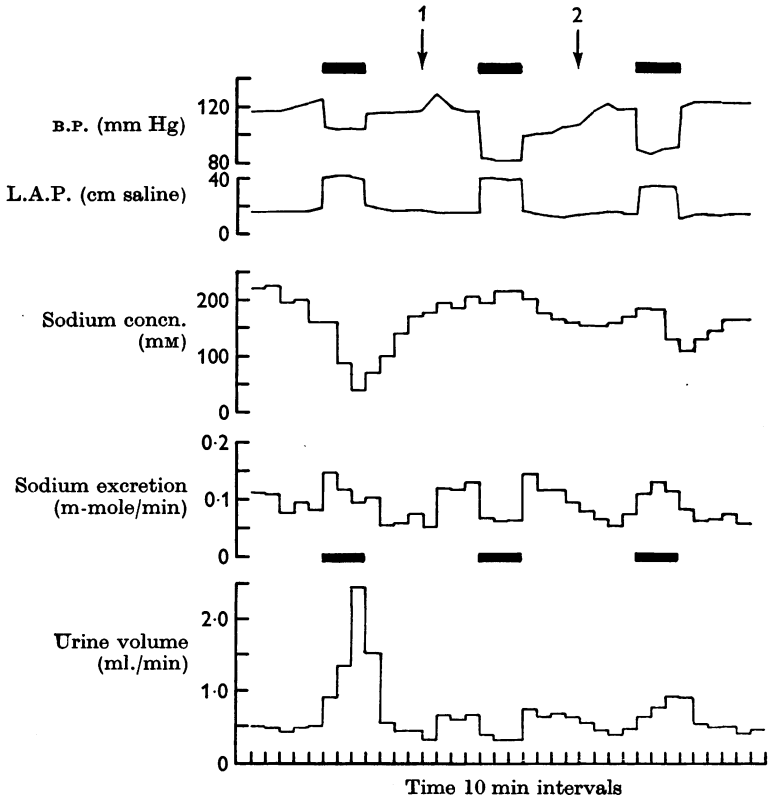

Fig. 7. Effect of an injection of local anaesthetic into the pericardial cavity. During the periods indicated by the bars the mitral orifice was obstructed by inflating a balloon in the left atrium. At the arrow marked '1', 2 ml. of a 2 % (w/v) solution of decicain was injected into the pericardial cavity. At the arrow marked '2', the pericardial cavity was washed out with saline.

evidence that the decicain had not remained only within the pericardial sac, because the diaphragm was paralysed throughout the experimental period; presumably the phrenic nerve, which is closely applied externally to the thin pericardium just anterior to the lung roots and pulmonary veins, had been anaesthetized by the decicain. The diaphragm was contracting again during the last control period after the decicain had been washed out.

DISCUSSION

Inflation of a balloon in the left atrium partially to obstruct the mitral orifice causes an increase not only in left atrial pressure but also in the pressures throughout the pulmonary vascular bed (Henry *et al.* 1956). The existence of receptors stimulated by distension of the intrathoracic parts of the circulation is well established and in the dog they have been described in the pulmonary arteries (Coleridge & Kidd, 1960) and at the junctions of the venae cavae and pulmonary veins with the atria (Coleridge *et al.* 1957). Henry *et al.* (1956) and Henry & Pearce (1956) have suggested that the first stage in the production of diuresis by mitral obstruction is the stimulation of receptors in the walls of the left atrium. This localization of the afferent mechanism to the left atrium was achieved by comparing the effects of mitral obstruction with the effects of snaring the extrapericardial pulmonary veins or with the effects of blocking the pulmonary circulation with multiple emboli. The latter two procedures were ineffective in producing diuresis. However, these three manoeuvres are not strictly comparable, and it was therefore desirable to use a technique which as far as possible would limit the stimulus to receptors in the left atrium and would not obstruct blood flow through the left atrium. The technique of distending small balloons in the pulmonary vein/atrial junctions of the left side of the left atrium appeared to meet these requirements.

It is known that the distension of small balloons in the left pulmonary vein/atrial junction stimulates the so-called left atrial receptors vigorously to discharge (Kidd *et al.* 1966), and also causes a reflex increase in heart rate (Ledsome & Linden, 1964, 1967). The afferent limb of this reflex is in the vagus nerves and the efferent limb is solely in the sympathetic nerves to the heart. The changes in heart rate resulting from distension of the pulmonary vein/atrial junctions reported in this investigation entirely support these conclusions. The magnitude of the increase in heart rate and the characteristic onset and decline of the heart rate changes during the 30 min period of distension of the pulmonary vein/atrial junctions in the fifteen dogs were the same as those previously reported (Ledsome & Linden, 1964). Additional confirmation of the previous report was observed when, after cutting both ansae subclaviae in five dogs, the increase in heart rate produced by pulmonary vein distension did not occur. This technique of distension of the pulmonary vein/atrial junctions did not obstruct the flow of blood through the left atrium; in fact, concomitantly with responses of large increases in heart rate, it was observed that the pressure in the left atrium fell (Ledsome & Linden, 1964).

The results reported in this paper leave no doubt that distension of the pulmonary vein/atrial junctions can cause a diuresis with characteristics

similar, in all respects except its magnitude, to the diuretic response to mitral obstruction. However, the small size of the response to pulmonary vein distension and indeed the difficulty in demonstrating a response at all was surprising, particularly since the technique does not obstruct blood flow or cause a fall in arterial pressure. Arndt, Reineck & Gauer (1963) described a few experiments in which mitral obstruction had caused a severe reduction in cardiac output and antidiuresis, and it seemed likely that a fall in cardiac output could limit the diuretic response to mitral obstruction (Gauer & Henry, 1963). Several explanations for the small size of the diuretic response to pulmonary vein distension should be considered. First, pulmonary vein distension affects mainly those receptors on the left side of the left atrium whereas mitral obstruction will affect all the receptors in the atrium. Secondly, the small balloons may not have provided an adequate stimulus to all the receptors even on the left side of the left atrium. It has been shown that this technique can increase the discharge from single receptors from a resting discharge of about 4 impulses/beat to about 30 impulses/beat (Kidd *et al.* 1966); mitral obstruction has been shown to increase the discharge of single receptors from 8 impulses/beat to 20 impulses/beat (Henry & Pearce, 1956). There will be great variation in the responses of individual receptors but it is likely that pulmonary vein distension is at least as effective as mitral obstruction in causing a high rate of discharge from some of the receptors. Thus, it is probable that pulmonary vein distension produced less than half as much increase as mitral obstruction in the total number of afferent impulses discharged into the vagus nerves. Evidence that some receptors were stimulated in both these groups of experiments is given by the fact that there was always an increase in heart rate during every test and it is likely that this increase in heart rate resulted from the reflex described above. Thirdly, the animals and/or the kidneys of these animals may not have been in a suitable state to produce a diuresis. This criticism may be applied to the first group of dogs, in which the control urine flows were low (average 0·3 ml./min, see Figs. 1 and 2), but it cannot be applied to the group in which mitral obstruction was shown to be highly effective. Fourthly, the possibility remains that mitral obstruction achieves its effectiveness by stimulating not only atrial receptors but also by acting through some additional mechanism.

Because it has been shown that distension of the pulmonary vein/atrial junctions caused a reflex increase in heart rate with the efferent pathway in the cardiac sympathetic nerves (Ledsome & Linden, 1964) and that stimulation of cardiac sympathetic nerves has been shown to cause diuresis (Gilmore, 1959), the effects of cutting the ansae subclaviae on the diuretic responses to left atrial distension have been studied. The ansae

subclaviae in the dog contain most if not all of the sympathetic accelerator fibres to the heart (Mizeres, 1958). In the series of dogs in which only distension of the pulmonary vein/atrial junctions was tested, cutting both ansae subclaviae, though abolishing the heart rate response, did not appear to affect the already small diuresis. Quantitation of such small diuretic responses is difficult, but it may be significant that one of the largest responses occurred in a dog with both ansae cut (Fig. 1). In the dogs in which mitral obstruction was tested, cutting both ansae subclaviae did not prevent the appearance of large diuretic responses. Although the average change in urine flow after cutting the ansae subclaviae was rather less than in the tests with the nerves intact, this difference was due mainly to one control test in which there was an exceptionally large diuresis (Table 1). Thus cutting the ansae subclaviae did not appear to affect the *relative* size of the diuretic response to mitral obstruction although the increases in heart rate produced by the manoeuvre were reduced. The diuretic response to mitral obstruction is therefore not dependent upon an increased activity in efferent cardiac sympathetic nerves or upon afferent impulses travelling in the ansae subclaviae, but the increase in heart rate caused by mitral obstruction is partly dependent upon impulses travelling in the ansae subclaviae.

Cutting the thoracic vagus nerves above the lung roots cuts all afferent fibres from the lungs travelling in the vagus nerves. In addition, cutting the left vagus nerve at the level of the upper border of the aorta prevents most of the reflex increase in heart rate induced by pulmonary vein distension (Ledsome & Linden, 1964) and probably cuts most of the afferent fibres from the left side of the left atrium. The majority of receptors lying on the left side of the left atrium have their afferent fibres in the left vagus nerve (Coleridge, Coleridge & Kidd, 1964). In the present experiments cutting the right vagus nerve above the lung root and the left vagus nerve at the level of the upper border of the aorta may have reduced, but did not prevent, the diuretic response to mitral obstruction. The diuretic responses to mitral obstruction with these nerves cut also compared favourably with the responses to pulmonary vein distension although about half the fibres from left atrial receptors had been cut. When, in addition, the right vagus trunk was cut or cooled in the neck, there was no diuretic response to left atrial distension caused by mitral obstruction and indeed urine flow decreased. These results allow several conclusions to be reached. First, the diuretic response to mitral obstruction does not depend upon changes in activity in afferent fibres from the lungs. Secondly, sufficient afferent fibres to allow a diuretic response join the right vagus nerve between the lung root and the neck. Thirdly, cutting the left vagus nerve at the upper border of the aorta and not in the‛neck cuts the thoratic vagus

nerve, the recurrent laryngeal nerve and the inferior cervical cardiac nerve (Mizeres, 1955), but leaves intact most efferent vagal fibres and most afferent fibres from pulmonary arterial baroreceptors, aortic baroreceptors and aortic chemoreceptors (Coleridge *et al.* 1964). Reduction of the response after nerve section at this level is most readily explained in terms of interruption of afferent fibres from the left side of the left atrium (from the left atrial receptors), which have been shown by pulmonary vein distension to be capable of contributing to the diuretic response. Fourthly, impulses in afferent fibres from intrathoracic receptors which join the left vagus above the level of the upper border of the aorta may or may not contribute to the diuretic response but are not alone capable of initiating it. Lastly, the fact that an intrapericardial injection of a local anaesthetic prevented the diuretic response to mitral obstruction suggests that sensory nerve endings or fibres close to the heart are involved in the diuretic response. Because of the distribution of the dye used with the anaesthetic, the receptors and nerve fibres most likely to have been affected by the local anaesthetic are the left atrial receptors and/or their afferent fibres.

The experiments were designed to examine whether stimulation of left atrial receptors was involved in the diuretic response to left atrial distension. They do not provide any information on either the nature of the agent acting upon the kidney to produce the diuresis or whether or not the diuretic response may be considered as a specific reflex. The results support the view (Henry *et al.* 1956) that stimulation of left atrial receptors can cause diuresis and that such stimulation is a major factor in the production of the diuretic response to mitral obstruction. The possibility is raised that the peculiar effectiveness of mitral obstruction as a stimulus might depend in addition upon a change in the stimulus to other receptors. However, the experiments described provide no support for such a theory; indeed it is possible to speculate that stimulation of left atrial receptors is the only stimulus necessary to evoke the characteristic response.

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