

THE POSSIBLE ROLE OF CARDIAC ATRIAL STRETCH  
RECEPTORS IN THE INDUCTION OF CHANGES  
IN URINE FLOW

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There is adequate evidence that changes in blood volume, unaccompanied by alterations in plasma osmotic pressure, will lead to compensating variations in urine flow (Metcalf, 1944; Welt & Orloff, 1951; Strauss, Davis, Rosenbaum & Rossmeis, 1951; Henry & Gauer, 1951; Zuidema, Reeves, Clark, Henry & Gauer, unpublished). It has been suggested that such changes in urine flow may be provoked by alterations in the 'fulness of the blood stream' (Peters, 1935). Receptors sensitive to variations in circulating blood volume have been postulated, and evidence that such receptors lie in the thoracic viscera, and specifically in the cardiac atria, has been provided (Gauer, Henry, Sieker & Wendt, 1954; Henry, Gauer & Sieker, 1956; Henry, Gauer & Reeves, 1956). These authors described experiments in dogs in which negative pressure breathing, designed to increase the thoracic blood volume selectively, was associated with a diuresis; positive pressure breathing was associated with antidiuresis. Distension of the left atrium alone by expansion of an indwelling balloon also resulted in a pronounced diuresis. The response to negative pressure breathing was abolished or reduced by section of, or cold-blocking, the vagus nerves (Henry, Gauer, Sieker, Wendt, Reeves & Lee, 1953). There is little evidence (Gruber, 1933) that vagus nerves could serve as the efferent pathways of the diuretic mechanism, but blocking of afferent fibres could explain the interference with the reflex.

Since the receptors sensitive to volume variations were believed to be in the atria, a search was made in the vagus nerves for afferent fibres from receptors affected by atrial distension. Such fibres have been described in the cat

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(Paintal, 1953*a*), with clear evidence that their receptors exist in the walls of both atria and respond to distension rather than pressure. These fibres were first described by Walsh & Whitteridge (1944), and their characteristics of discharge were more fully described by Whitteridge (1948). He deduced that the receptors were situated in the pulmonary circulation, a belief which appeared to be substantiated by the good correlation between pulmonary arterial pulse pressure and activity of the fibres (Pearce & Whitteridge, 1951). By mechanical stimulation at the site of the receptors Paintal (1953*a*) established, however, that they were in the atrial walls. He designated their fibres as type B to distinguish them from the earlier described venous fibres (Whitteridge, 1948; Neil & Zotterman, 1950; Dickinson, 1950), which were referred to as type A and which arise in receptors sensitive to pressure.

The first purpose of the work reported here was to show the existence of atrial type B fibres in the dog, and to confirm that the stimulating mechanism was distension rather than transmural pressure increase. The second purpose was to demonstrate that the manoeuvres shown to be associated with diuresis in the dog would also increase the activity in these fibres. Early results of experiments with this objective are published in a preliminary report (Pearce & Henry, 1954). A third purpose was to show that changes in circulating blood volume, which are known to alter left atrial size (Salzman, Zuidema & Edelberg, 1955) are followed by corresponding changes in activity of the fibres. Infusions of saline have been shown (Whitteridge, 1948) to increase the activity of these fibres in the cat. A final objective was to compare the degree of cold block of the vagus nerves necessary to abolish the diuretic response to balloon inflation with that required to block nervous conduction in the fibres.

#### METHODS

*General procedure and cardiovascular recording.* Dogs were used, anaesthetized with 1 mg/kg of morphine and 70–80 mg/kg of chloralose; the anaesthetic level was maintained with chloralose at sufficient depth to prevent involuntary limb movement. After artificial ventilation was begun the chest was opened and a small rubber balloon (capacity 20 ml.), tied over the end of wide polythene tubing, was inserted through the auricle into the left atrium. In some animals snares were passed around the right and left pulmonary vein groups; the ends of the snares were brought to the outside of the chest within an airtight rubber drain sleeve. The chest wound was then closed and intrapleural air removed. The intrathoracic operations are fully described by Reeves (Reeves, Gauer & Henry, 1956), for whose operative skill and co-operation we are indeed indebted.

Pressures in the right atrium, pulmonary artery (PAP) and femoral artery (AP) were transmitted through saline-filled polythene catheters to bonded resistance wire strain gauges. Left atrial pressure (LAP) was recorded similarly from a catheter which had been inserted into the atrium with the balloon. The natural frequency of these systems was over 80 c/s, and the time for transmission of the atrial pressure pulse to the gauge was about 5 msec. The strain gauges were connected to an oscillograph for viewing and recording pressure changes, or to an oscilloscope through condenser coupling for simultaneous recording of fibre discharge and atrial pressure. The time constant of the coupling was about 50 msec, an arrangement producing some distortion of the LAP pulse contour and magnitude in the simultaneous recordings but ensuring that the pattern remained on the screen.

*Manoeuvres used to alter fibre activity.* The techniques of application of negative pressure breathing (NPB) (Gauer *et al.* 1954), balloon distension and partial pulmonary vein ligation (Henry, Gauer & Reeves, 1956) are described in connexion with experiments on urine flow. The latter two procedures were used to detect some higher threshold fibres and to distinguish between those from the right and left atria. Infusions of blood, 6% bovine albumin in physiological saline and saline alone were injected into a forelimb vein in 50 ml. aliquots warmed to body temperature. Blood was withdrawn from the femoral artery.

*Vagus nerve block and urine collection.* During the experiments in which urine flow was measured, the urine was collected into a burette from a urethral catheter; the burette was read and emptied every 10 min. The vagus nerves were partially surrounded and in contact with silver cooling blocks through which flowed cold ethylene glycol from a reservoir; the degree of cooling was regulated by governing the rate of flow through the block, and measured with two thermocouples, one junction of each soldered into each block. A similar cooling procedure was used on the left side only, below the point of recording from vagus strands, in order to determine the temperature which blocked conduction in atrial fibres.

*Recording of electrical activity in the vagus.* The technique of dissection of the vago-sympathetic trunk, with minor modifications, followed that already described (Whitteridge, 1948; Paintal, 1953*a*). The left cervical trunk was exposed through a mid-line incision; the flap of skin was retracted to form a trough which could be filled with warm liquid paraffin. After the nerve had been freed from the carotid sheath, a short length of the tough perineurium was removed under paraffin with a fine scissors. A binocular  $\times 15$  microscope was used and a bright spot lamp provided both light and heat. Bleeding from the cut sheath had to be checked constantly with cotton-wool pledgets. When a length of about 2 cm of nerve was visible, small strands were plucked from the proximal end, cut across with a razor blade knife and separated downwards with this knife. The strand was then laid over a pair of silver input electrodes and wrapped around the second electrode. Great care had to be taken during separation of the strand as any tugging or bending of the fibre usually rendered it inactive. Strands were either silent, or showed irregular low voltage activity, or contained higher voltage spikes of afferent fibres of various origins. The silent strands and those showing only sporadic impulses were discarded. Active strands showing a cardiac rhythm were subdivided in an attempt to get single unit preparations wherever it was not felt that further interference with the fibre would lead to complete damage. It is stressed that a single unit preparation arrived at by this method may contain many nerve fibres, only one of which is undamaged and active.

The input electrodes led to conventional push-pull condenser-coupled amplifiers connected to the Y plates of the upper beam of a double-beam cathode-ray oscilloscope. The simultaneously recorded e.c.g. (lead II) was displayed on the lower beam and the QRS complex was used to trigger the sweep of both beams; the output from the strain gauge registering left atrial pressure could be switched to operate the lower beam in place of the e.c.g. Recording from the oscilloscope or the oscillograph was made using moving film or sensitive paper and stationary spots.

## RESULTS

### *Characteristics of atrial stretch fibres*

In fifteen dogs seventeen fibres with a discharge characteristic of atrial type B receptors were found. The fibres showed both a cardiac and a respiratory rhythm, with increased activity or cessation of discharge during artificial inflation of the lungs. Where LAP was recorded, in no instance was there a discharge of impulses in time with the point of maximum pressure of the 'a' wave (corresponding to atrial systole), although occasionally there were a few impulses in time with the beginning of the 'a' wave or coincident with the 'c'

wave (corresponding to early ventricular systole). The main burst of impulses always coincided with the 'v' wave (corresponding to atrial filling and passive emptying). These features are illustrated in Figs. 1 and 3, and the usual pattern of discharge frequency, plotted against time of occurrence of impulses, is shown in Figs. 2 and 4. The plot was usually a single curve, occasionally with

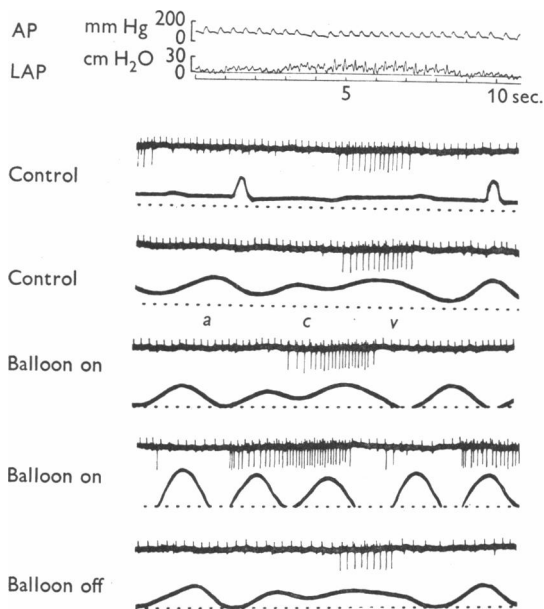


Fig. 1. The uppermost section shows the effect of distension of the indwelling left atrial balloon on AP, arterial pressure and LAP, left atrial pressure, each recorded by strain gauge and oscillograph; the balloon was distended during the period 3-8 sec. The next five sections record the response of atrial stretch fibres to distension of left atrial balloon. The first 'control' record shows, from above downwards, the activity in two left atrial stretch fibres seen below the base-line, the e.c.g. from lead II and timing marks at 60 c/s. The same fibre activity is seen in the next section with LAP simultaneously recorded from the oscilloscope; the component waves are identified. As the balloon volume increases during the period corresponding to 3-7 sec in the top record so do the frequency and duration of fibre discharge. On collapse of the balloon the LAP returns to control values and the fibre discharge reverts to a subnormal frequency.

two humps and often irregular at higher frequencies. The average peak frequency during inspiration was 90/sec, occurring about 90 msec after the 'T' wave of the e.c.g. and approximately coincident with the peak of the LAP 'v' wave. The small delay between the peak frequency and the peak of the 'v' wave may be explained by a delay in arrival of the pressure pulse at the strain gauge and a 'phase shift' produced by the condenser coupling between the strain gauge output and the oscilloscope. The average number of impulses

during inspiration was 8/beat. In some animals the discharge was of longer duration, having as many as 15 impulses/beat and beginning in time with the 'c' wave of the pressure tracing.

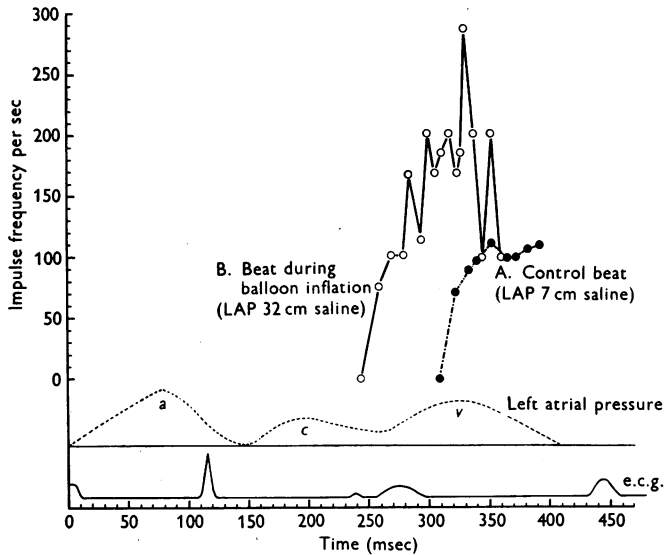


Fig. 2. Plot of impulse frequency against time for the same fibre over two heart beats (B) during and (A) following balloon distension. Data were obtained from records shown in Fig. 1. Time of occurrence of impulses in each beat is measured from the P wave of the corresponding e.c.g. The LAP and e.c.g. corresponding to B are represented below; distension of the balloon increases the heart rate, hence the peak frequency occurs earlier in the cardiac cycle than during the control period.

#### *Effect of balloon distension*

In thirteen experiments distension of the balloon in the left atrium produced considerable increases in the activity of the atrial fibre isolated. The increased activity, which began immediately, was evidenced by increased number of impulses per beat (average 20), increased peak frequency (average 160) and increased duration of discharge. The peak frequency usually occurred earlier in the cardiac cycle, corresponding in part to the increased heart rate. In one experiment the peak frequency reached 500/sec; this suggests a maximum spike duration consistent with the view that the fibres were at least of medium diameter, recalling Paintal's observation (1953*b*) that the conduction rates of atrial stretch fibres in the cat are in the intermediate range. Some of these features are seen in Figs. 1-4. Often the frequency/time plot showed two peaks with an earlier high frequency burst corresponding to the 'c' wave. This discharge, associated with a high inflexion in the LAP tracing, may have been produced by regurgitation of blood through the mitral valve rendered incompetent by the distended balloon. There was never a discharge corresponding

to the peak of the 'a' wave; at this point the atrial pressure was greatest but the volume least. The activity returned to or below control levels after balloon collapse (Figs. 1 and 3).

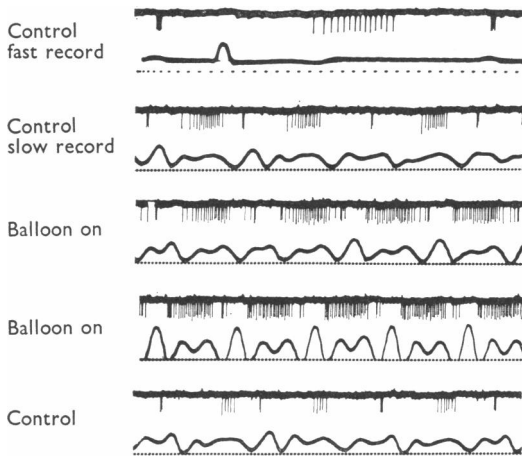


Fig. 3. The effect of balloon distension on left atrial stretch fibre activity, upper line, with e.c.g. or LAP below. Timing marks are at 60 c/s. The slow records clearly show that the 'a' wave of atrial systole is unaccompanied by impulse discharge, in spite of the great increase of atrial pressure at this time.

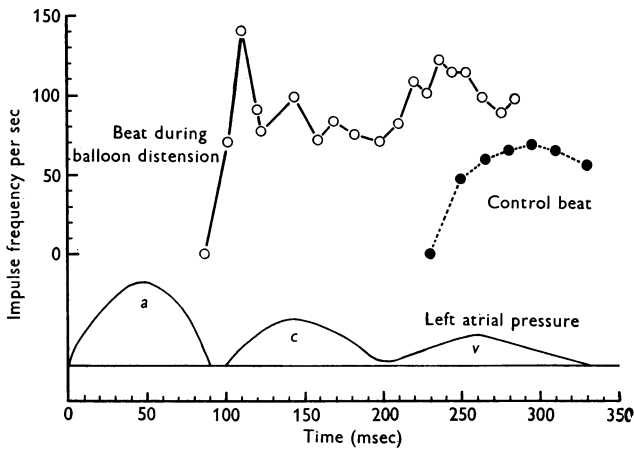


Fig. 4. Frequency time plot of one of the left atrial fibres shown in Fig. 3. During the period of balloon distension there is an early high frequency burst of impulses possibly due to mitral regurgitation.

Oscillograph records of left atrial pressure, taken during normal respiration and a following balloon distension, were compared with oscilloscope records of left atrial stretch fibre activity, taken immediately before, during similar periods of respiration and balloon distension. Although the recordings were

not taken simultaneously, for technical reasons, the comparison showed that a better relation existed between the level of fibre activity and the rate of rise or pulse pressure of the 'v' wave than with mean atrial pressure.

No clearly identified right atrial fibres, either type A or type B, were encountered in these dissections of the left vagosympathetic trunk.

#### *Effect of pulmonary vein ligation*

Tightening of these ligatures gave no consistent or marked change in the behaviour of six left atrial stretch fibres. In several cases the discharge was reduced or abolished. This procedure has previously been shown to cause marked rises in PAP with little change in LAP (Henry, Gauer & Reeves, 1955), and the same effects were observed in these experiments.

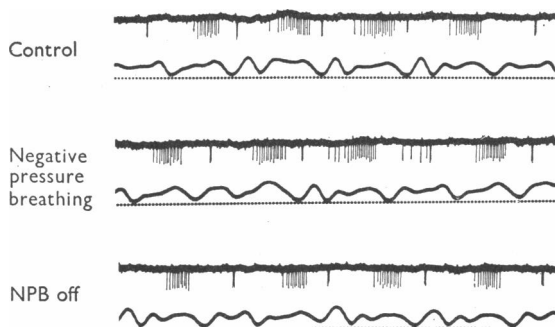


Fig. 5. Effect of NPB on discharge in left atrial stretch fibres. There is a moderate increase in activity. The decrease in fibre activity below control values after cessation of the NPB was a consistent finding.

#### *Effect of negative pressure breathing (NPB)*

The activity of four left atrial stretch fibres was followed before, during and after NPB. A clear result is shown in Fig. 5. The increase in activity was small, with an average increase of about 15% in mean number of impulses per beat over several respiratory cycles. The response of these fibres to balloon inflation, which increased the LAP much more, or to momentary suction on the trachea, which caused a greater fall in intrathoracic pressure, was greater than the increased activity evoked by NPB.

#### *Effect of bleeding and infusion*

Each of these procedures was carried out during recording from eight left atrial stretch fibres. There was considerable variability in the resulting changes in level of activity, but on occasion alterations in the circulating blood volume by as little as an estimated 5% produced obvious effects on fibre discharge (Fig. 6). Following serial haemorrhages each decrease in activity was partially restored after a lapse of several minutes, presumably owing to cardiovascular

adjustments to decreased vascular pressures. Restoration of blood volume with whole blood produced an increase in fibre activity toward normal. In one experiment the infusion of 100 ml. of 6% bovine albumin in physiological saline resulted in continuous discharge in a typical left atrial fibre (Fig. 7). The increase in activity of fibres with infusions of about 20% of estimated blood volume was considerably more than that observed with NPB at -10 cm water.

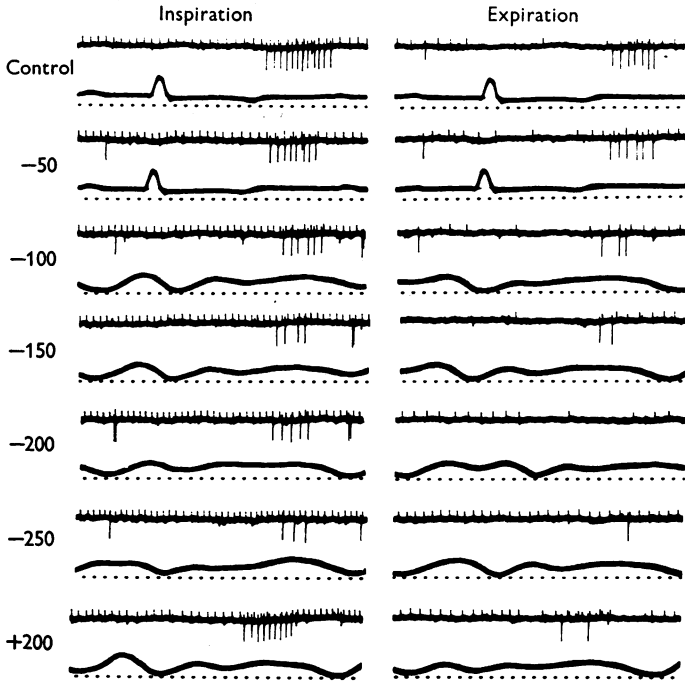


Fig. 6. Effect upon left atrial stretch fibre activity of serial haemorrhages and blood re-infusion. The greatest (inspiration) and least (expiration) discharge per beat were selected from a complete respiratory cycle. Negative numbers represent the total loss of blood in ml. up to that time; positive number indicates total re-infusion.

*Effect of cooling of vagi on diuretic response to balloon inflation and on conduction in atrial stretch fibres*

In six experiments the diuretic response was abolished when the vagi were cooled to between 8 and 12° C. The response was usually again elicited after the vagi were allowed to resume body temperature. Such results are shown in Fig. 8A.

Six left atrial fibres, in different experiments, were blocked by temperatures ranging from 4.5 to 12° C with an average value of 6° C. Wedensky inhibition began to reduce the discharge frequency at temperatures on average 6° C higher. The effect of cooling on a double fibre preparation is seen in Fig. 8B.



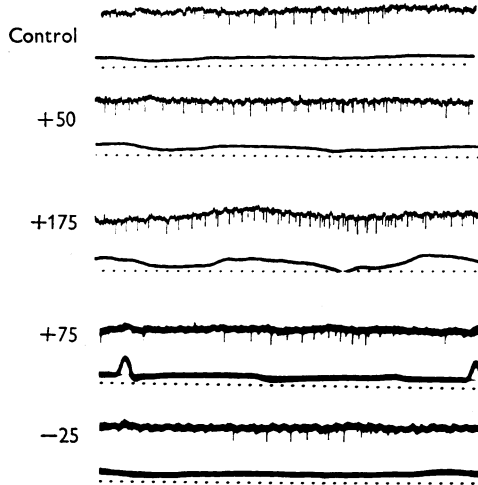


Fig. 7. Effect upon left atrial stretch fibre activity of serial infusions of 6% bovine albumin in 0.9% saline followed by withdrawal of 100 ml. blood twice in succession. Numbers as in Fig. 6. The LAP is recorded, except in the fourth section where the e.c.g. is substituted for the pressure tracing. Note that the discharge becomes almost continuous after infusion of 50 ml. and that the activity returns to a level below normal after removal of blood approximately equivalent in volume to the amount of infusion.

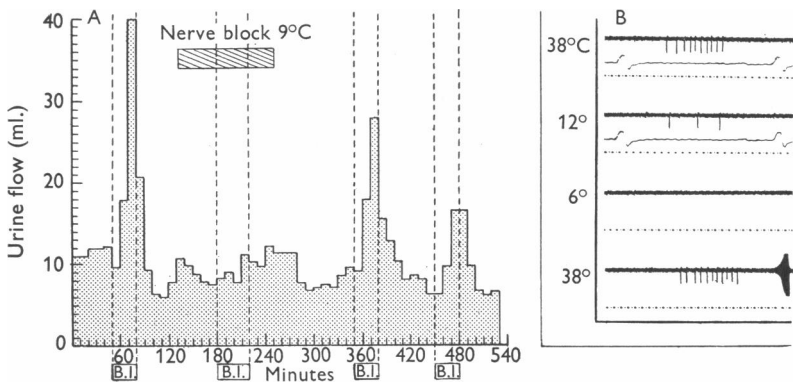


Fig. 8. A: the increase in urine flow (ordinate, ml./10 min) in response to distension of a left atrial balloon (B.I.) is abolished by cooling the vagi to 9°C. B: conduction in two left atrial stretch fibres is blocked at about 12 and 6°C. The spikes have been retouched. The blocking temperature range is approximately the same as that which prevents the diuretic response to distension of the atrial balloon.

## DISCUSSION

The existence of atrial type B fibres in the dog can be concluded from the similarity between the characteristics of discharge in these fibres and those of the fibres described by earlier workers in the cat. The prompt increase in fibre activity on inflation of the indwelling left atrial balloon, and the failure of the discharge to increase on tightening the pulmonary venous ligatures, confirm that the receptors lie in the wall of the atrium—or possibly in the pulmonary veins on the atrial side of the ligatures.

The absence of a burst of impulses in association with the 'a' wave of the LAP tracing, when the pressure at this time is higher than at any other point in the cardiac cycle, is consistent with Paintal's view (1953*a*) that the receptors are stretch- rather than pressure-sensitive. At atrial systole the volume of the chamber is least, whereas just before the opening of the auriculo-ventricular valves, when the discharge frequency is greatest, the volume is also greatest. Electrokymographs of the left atrium (Andersson, 1952) may bear a strong resemblance in shape to the frequency/time plot of an atrial stretch fibre. If the origin of the 'c' wave of the venous pressure tracing is a bulging into the atrium of the atrio-ventricular valve (Wiggers, 1923), this could give rise to a sudden stretch of the chamber, accounting for the short-lasting high frequency burst occasionally seen in time with the 'c' wave. The inconsistent finding of a few impulses occurring in time with the beginning of the 'a' wave has been described before, in the cat with open chest, by Paintal (1953*a*) and suggested by him to have been 'brought about by a change in the position of the heart'. In our experiments it is possible that a momentary stretch of one portion of the atrium, rendered unnaturally immobile by the indwelling balloon, occurred as the atrium began to contract in another portion.

Although it is clear that these receptors discharge during atrial filling, and show increased activity during exaggerated distension of the atrium or increase in venous return to the heart, the precise nature of the stimulus cannot be determined from these experiments. The impulse frequency plot does not always correspond in shape or timing with the 'v' wave of the atrial pressure curve, although a delay in arrival of the recorded peak of the 'v' wave can be accounted for. The closer relation of levels of fibre activity to the pulse pressure of the 'v' wave than to the mean atrial pressure is not inconsistent with the view that atrial stretch fibres respond to atrial filling. Changes in mean pressure might produce variations in atrial distension within a range below the threshold of the receptors, while diastolic distension apparently always exceeds the threshold providing the circulating blood volume is adequate. Although atrial stretch receptors in the cat have been shown to adapt slowly (Paintal, 1953*a*), the initial frequency might depend on the rate of distension as Landgren (1952) has shown to be the case with carotid sinus baroreceptors.

This would explain the relation between pulse pressure and rate of rise of the 'v' wave and number of impulses during a burst of short duration. It would then follow that rate of filling, as well as degree, might influence the discharge. It is conceivable also, since the atria are actively changing size by contracting, as well as passively expanding, that the filling volume of the atrium can only be appreciated by the integration of information from both stretch and pressure measuring receptors.

Receptors buried in the atrial wall, or extended on either surface of it, and attached at both ends, would be expected to respond only to the variations in distension of the atrium which accompany changes in filling. Subendocardial and perimuscular sensory arborizations of vagal origin, which could qualify for this role by their location, have been described in the dog (Nonidez, 1937; Woollard, 1935). Other receptors described, however, resemble known pressoreceptors and could be considered to belong to type A fibres. Further histological study of receptors in the atrium, after localization by electrophysiological methods, is needed.

Both NPB and distension of the indwelling left atrial balloon produce diuresis, and both procedures increase the activity of atrial stretch fibres. The increase in response to NPB is small compared with the exaggerated discharge resulting from balloon inflation; the distension produced by the balloon is, however, restricted to one atrium. This may explain why the diuresis with NPB is often as great as that following balloon inflation. Small losses of blood are often associated with antidiuresis (Zuidema *et al.* unpublished) and are also accompanied by a considerable reduction in atrial stretch fibre discharge. Expansion of the blood volume with such isotonic infusions as plasma (Metcalf, 1944), albumin solution (Welt & Orloff, 1951), saline (Strauss *et al.* 1951) and blood (Zuidema *et al.* unpublished) has been shown to result in diuresis. Such expansion of the circulating blood volume results in increased activity of these fibres, sometimes to the extent of producing a continuous discharge. Although there is as yet no experimental evidence, it is likely that other procedures which alter circulating blood volume and result in changes in urine flow (Table II, Gauer *et al.* 1954) will also produce related changes in activity of atrial stretch fibres.

The above suggestions of a direct relation between augmented atrial stretch fibre activity and increased urine flow have been in part subjected to the test that vagotomy, or cold block of the nerves, should abolish the relation. The response to balloon distension was prevented by cold block of the vagi. Also, in the case of NPB, the cold block usually abolished but occasionally only reduced the diuretic response (Henry *et al.* 1953). It is of interest that the blocking temperature range was close to that which partially or completely blocked conduction in the axons from atrial stretch receptors. Conclusions from this finding must be drawn with caution, however, in the light of Paintal's

demonstration (1953*b*) of the wide range of conduction rates of fibres of a given origin, and evidence of the wide range of blocking temperatures of fibres of a given function (Widdicombe, 1954).

It has been shown recently in the dog that vagotomy does not abolish the diuretic response to isotonic infusions of bovine albumin in Ringer-Locke solution (Pearce & Roberts, 1955; also unpublished notes). This finding does not rule out the possibility that atrial receptors serve as one group of sensory endings concerned in the reflex production of diuresis by blood volume expansion; but it indicates that there may be other receptors or other pathways for the atrial receptors. The possibility also exists that the bovine albumin solution produced a diuresis by some other means than simple expansion of the plasma volume, and experiments are to be done to determine the effect of vagotomy on the diuretic response to infusion of blood and on the anti-diuretic effect of haemorrhage. The speculation that carotid sinus endings might serve as a second set of stretch receptors had been suggested by the finding that stretch receptors exist in the sinus (Landgren, 1952). The diuresis following infusion of isotonic bovine albumin solution in dogs was, however, not uniformly abolished by both vagotomy and denervation of the carotid sinuses. It is necessary to conclude that, in addition to the atrial receptors with their fibres in the vagus, the body may be provided with other receptors or pathways by which it receives information which makes possible the regulation of blood volume by the control of urine flow.

#### SUMMARY

1. Afferent vagal fibres, with the discharge characteristics previously described for cardiac atrial stretch fibres in the cat, have been isolated in the dog.

2. The increase in activity of such fibres from the left atrium on distension of an indwelling atrial balloon, and the absence of any augmented activity during partial obstruction of the pulmonary veins, confirms that the receptors lie in the atrium or possibly in the pulmonary veins near their mouths.

3. The absence of discharge in the fibres during atrial systole, when the pressure is greatest, and the close relation of the peak discharge to maximum atrial filling in late diastole, when the volume is greatest, support the conclusion that the receptors respond to stretch rather than to pressure.

4. Several manoeuvres known to produce diuresis in the anaesthetized animal, distension of a balloon in the left atrium, negative pressure breathing, or expansion of the blood volume with isotonic infusions, each increase the activity in these fibres. Small haemorrhages, known to produce antidiuresis, decrease the activity in the fibres.

5. The range of cooling temperature of the vagi which is necessary to prevent the diuretic response to balloon distension and negative pressure

breathing is close to that found in a small series to be necessary to block conduction of left atrial fibres.

6. It is suggested that the filling volume of the cardiac atria, which bears a relation to the circulating or thoracic blood volume, could be appreciated by integration of information from both stretch and pressure receptors.

7. It is proposed that cardiac atrial stretch receptors serve as one sensory mechanism in a reflex regulation of blood volume by control of urine output.

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