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REFLEX EFFECTS ON THE HEART OF STIMULATING LEFT ATRIAL RECEPTORS

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SUMMARY

1. Stimulation of left atrial receptors, by distension of the pulmonary vein/left atrial junctions, is known to cause a reflex increase in heart rate; the efferent pathway is known to be solely in the sympathetic nerves.

2. In expectation of a concomitant positive inotropic response the effect of stimulating the left atrial receptors on the inotropic state of the left ventricle was studied, using as a known sensitive index of inotropic changes the maximal rate of rise of pressure in the left ventricle (dP/dt max).

3. Stimulation of left atrial receptors resulted in an increase in heart rate but there were no significant concomitant changes in dP/dt max.

4. It is concluded that activity in this discrete efferent pathway does not include an inotropic effect on the left ventricle and therefore the reflex involves only those sympathetic nerves which innervate the sinu-atrial node.

5. The possible function of atrial receptors in the regulation of heart volumes is discussed.

INTRODUCTION

Ledsome & Linden (1964) reported a reflex increase in heart rate following distension by small balloons of the pulmonary vein/left atrial junctions in anaesthetized dogs. The afferent pathway of this reflex was found to be in the vagi and the efferent path was solely in the cardiac sympathetic nerves. The same reflex was elicited again during a further investigation in which a pouch of the left atrium was distended by pulsatile pressure changes (Ledsome & Linden, 1967). From studies similar to the above but in which action potentials were also recorded from the vagal nerves in the neck it was suggested that the receptors most likely to be involved in this reflex are those situated in the subendocardial tissue at the junctions of the pulmonary veins and left atrium (Kidd, Ledsome & Linden, 1966).

It is known that the effect of activity in the cardiac sympathetic nerves usually includes an inotropic as well as a chronotropic effect (e.g. Sarnoff, Brockman, Gilmore, Linden & Mitchell, 1960*a*). Therefore it would be expected that a positive inotropic effect would accompany the reflex increase in heart rate observed in response to distension of the pulmonary vein/atrial junctions.

The present investigation was designed to determine whether a positive inotropic response accompanied the increase in heart rate during this reflex response. Using a method previously shown to give a sensitive index of positive inotropic changes (Furnival, Linden & Snow, 1970) it was found that no positive inotropic effect was associated with the reflex increase in heart rate which resulted from distension of the pulmonary vein/left atrial junctions. A preliminary account of this investigation has been given (Furnival, Linden & Snow, 1968*b*).

METHODS

Dogs weighing between 14 and 21 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 of each animal and general anaesthesia was induced by intravenous infusion of a solution of α-chloralose (British Drug Houses Ltd., Poole, Dorset) 0·1 g/kg body weight (1 g dissolved in 100 ml. of a solution of sodium chloride (0·9 g/100 ml.)). Subsequently a steady state of light anaesthesia was maintained by infusion every 15 min of the solution of α-chloralose in a dose of about 1 ml./kg. As soon as possible after induction of anaesthesia the trachea was cannulated and artificial ventilation was started using a mixture of 40 % oxygen in nitrogen humidified at room temperature and supplied from a Starling 'Ideal' pump; the ventilation was adjusted so as to maintain the P_{CO_2} of arterial blood at about 40 mm Hg. In each animal when the chest was opened a resistance of 3 cm of H_2O was placed in the outlet of the respiratory pump.

The left side of the chest was opened in the fifth intercostal space and the lung retracted laterally. A small rubber balloon about 3 mm long, coated with silicone (Repelcote; Hopkin and Williams, Chadwell Heath, Essex) and attached to a nylon catheter (1 mm bore) was inserted into each of the three pulmonary veins and tied so that its tip lay at the junction of the pulmonary vein with the left atrium. The pulmonary vein/left atrial junctions could then be distended by injecting into each balloon 1·0 ml. of a solution of sodium chloride (0·9 g/100 ml.) at 38° C. Soft strings were placed around the roots of the lobes of the left lung and tied immediately behind the balloon catheters thus occluding all structures within the left lung root. The balloon catheters were led out of the chest and clamped.

Pressures in the cardiovascular system were recorded through metal cannulae ('Inconel'), 1·5 mm bore; Johnson Matthey & Co., London), treated with a solution of dialkyl dimethyl ammonium chloride ('Arquad'; Armour Hess Chemicals, Leeds Ltd.) as a non-wetting agent, inserted into the right femoral artery and the left ventricle through the apical dimple. To each of the two cannulae was attached a Statham strain gauge (model P 23 Gb; Statham Inst. Co., Inc., Puerto Rico) and after amplification by means of a carrier amplifier (model 423/1; S.E. Laboratories,

Feltham, Middlesex) the pressure was recorded using a direct-writing U.V. light recorder (S.E. Laboratories Ltd.). The frequency response of the system recording arterial pressure, obtained by the method of Ardill, Fentem & Welland (1967), was flat (± 5 %) to better than 60 c/s and that of the short metal cannula inserted into the left ventricle to better than 80 c/s. The methods of obtaining the rate of change of pressure in the left ventricle using an analogue differentiator and of using this measurement as an index of the inotropic response of the left ventricle have been described previously (Furnival *et al.* 1970). The strain-gauge manometers were calibrated in a stepwise manner using mercury and saline manometers; zero pressure for each strain-gauge manometer was recorded post mortem as the pressure at the cannula tip with the tip free in air. During the surgical procedures, which lasted about 2 hr, the animals received a slow infusion of Dextran 150 injection B.P. in 5 % (w/v) dextrose (Dextraven; Fisons Pharmaceuticals Ltd., Loughborough) of up to 8 % of their estimated blood volume (1·0 l. for each 13 kg body weight). The electrocardiogram was recorded from leads attached to the right foreleg or chest wall and left hind leg. The heart rate was recorded by means of a cardiotachometer (Gilford Instrument Co., Oberlin, Ohio, U.S.A.) triggered by the output of the amplifier used in recording arterial pressure. All heart rates included in the results were obtained by counting the recorded QRS complexes of the electrocardiogram for at least 30 sec. The oesophageal temperature was recorded from a thermistor probe (Yellow Springs Instrument Co. Inc., Yellow Springs, Ohio, U.S.A.) and maintained at 37·5° C (± 1) by adjusting heating lamps above and beneath the animal. Samples of blood were withdrawn anaerobically from a catheter in the left femoral artery with its tip in the aorta into warm syringes in which the dead space was filled with heparin (Pularin; Evans Medical Ltd.; 1000 i.u./ml.). The blood was transferred immediately to electrode systems and the P_{O_2}, P_{CO_2}, pH and bicarbonate concentration in the blood were measured; methods for the determination of these parameters have been described previously (Norman, Ledsome & Linden, 1965; Linden, Ledsome & Norman, 1965).

The effects of distension of the pulmonary vein/left atrial junctions were estimated in the following way. A control record was made during steady-state conditions before distension from which the heart rate, the maximum rate of change of pressure in the ventricle (dP/dt max) and mean arterial pressure were measured. All three balloons were then distended each with 1 ml. of warm saline and, after allowing 1–3 min for steady-state conditions to be attained, a second record was made. The saline was then withdrawn from the balloons and during steady-state conditions about 3 min after distension a second control record was made. The mean of the values obtained in the two control periods (i.e. before and after distension) was then subtracted from the value obtained during the period of distension and thus values for the increase in heart rate and the increase in dP/dt max resulting from distension of the balloons were obtained.

RESULTS

When recording began about 2 hr after the induction of anaesthesia, the arterial pressure was 140·0 mm Hg (mean; S.D. ± 15·2; range 110–170) the heart rate was 131·3 beats/min (mean; S.D. ± 14·8; range 110–162) and dP/dt max was 3614 mm Hg/sec (mean; S.D. ± 1027; range 1470–5810). In arterial blood the pH was 7·38 (mean; S.D. ± 0·029; range 7·34–7·43), the P_{CO_2} was 38·3 mm Hg (mean; S.D. ± 2·9; range 35–45) and the P_{O_2} was 202 mm Hg (mean; S.D. ± 22; range 170–242).

Changes in heart rate and dP/dt *max during pulmonary vein/left atrial distension*

In twelve animals the effect of thirty-seven distensions of the pulmonary vein/left atrial junctions was observed. An example of the records obtained before, during and after distension in one dog is shown in Fig. 1. Each panel shows a record of femoral artery pressure, left ventricular pressure at a high gain to show the end-diastolic pressure in the left ventricle and at a low gain to show the whole wave form, together with the rate of change of pressure (dP/dt) in the left ventricle. In this experiment the heart rate

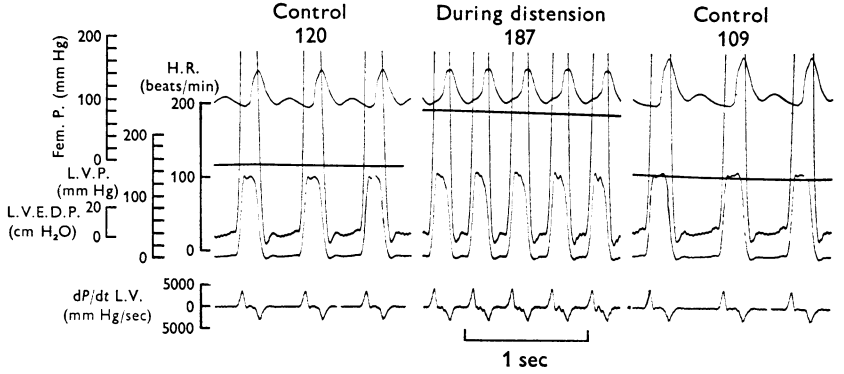

Fig. 1. Records from one dog showing the effect of distending the pulmonary vein/left atrial junctions. From above downwards: Fem. P., pressure in the femoral artery: H.R., heart rate; L.V.E.D.P., end-diastolic pressure in the left ventricle; L.V.P., pressure in the left ventricle; dP/dt L.V., rate of change of pressure in the left ventricle. The number above each panel is the heart rate in beats/min. First panel, control; second panel, during distension of the pulmonary vein/atrial junctions; third panel, 3 min after release of distension of the pulmonary vein/atrial junctions.

before distension was 120 beats/min and during distension rose to 187 beats/min before returning to 109 beats/min about 3 min after distension. The arterial pressure showed little change, the mean values being 108, 115 and 115 mm Hg before, during and after distension. As can be seen from the records only small changes occurred in dP/dt max, which rose from 3519 mm Hg/sec before distension to 4071 mm Hg/sec during distension and returned to 3833 mm Hg/sec after distension; a mean increase of 395 mm Hg/sec.

The results obtained in all thirty-seven distensions in twelve dogs are shown in Fig. 2; the increases in heart rate obtained during distension of balloons were accompanied by only small changes in dP/dt max and some of those changes were decrements. There was no significant correlation ($r = 0{\cdot}13; 0{\cdot}4 < P < 0{\cdot}5$) between changes in heart rate and in dP/dt max.

During the thirty-seven experiments the heart rate during the control periods was 148 beats/min (mean; S.D. ± 24; range 107–217). During distension of the balloons the heart rate rose to 169 beats/min (mean; S.D. ± 27; range 117–231); thus the average increase in heart rate during distension was 21 beats/min (range 6–90). The greatest increase in heart rate (90 beats/min) occurred in a dog where the mean control rate was 123 beats/min and during distension the heart rate rose to 213 beats/min.

The systemic arterial pressure in these animals during the control periods was 131 mm Hg (mean; S.D. ± 19; range 102–173). In fourteen experiments distension was accompanied by an increase in mean arterial pressure of 6·5 mm Hg (mean; range 1–16), in seventeen distensions the arterial pressure fell 9 mm Hg (mean; range 1–24) and in six distensions there was no change in mean arterial pressure. In some dogs the changes in arterial pressure during distension of the balloons were consistently an increase or a decrease but in others there was no consistent change, e.g. in one animal arterial pressure decreased 10 mm Hg and increased 12 mm Hg during two consecutive distensions, each of which resulted in the same increase in heart rate.

The control values of dP/dt max recorded before and after distension of the balloons were used to give a mean control value. In all thirty-seven distensions the control dP/dt max was 4128 mm Hg/sec (mean; S.D. ± 939; range 2553–6210). In twenty-eight distensions the rise in heart rate was accompanied by a very small increase in dP/dt max of 290 mm Hg/sec (mean; range 69–828); and in five distensions there was a small decrease in dP/dt max of 149 mm Hg/sec (mean; range 36–414); in the remaining four distensions there was no change in dP/dt max when the balloons were distended. Thus in all experiments during distension of the pulmonary vein/left-atrial junctions the mean change in dP/dt max was an increase of only 193 mm Hg/sec.

The greatest change in dP/dt max during any one distension of the balloons was an increase of 828 mm Hg/sec which accompanied an increase in heart rate of only 13 beats/min. The greatest increase in heart rate observed during distension (90 beats/min) was accompanied by an increase in dP/dt max of only 276 mm Hg/sec.

Changes in dP/dt *max resulting from changes in heart rate*

These results show that only very small changes in dP/dt max accompanied the reflex increase in heart rate induced by distension of the pulmonary vein/left atrial junctions; indeed the changes were less than those which might have been associated with changes in heart rate alone, e.g. during electrical pacing of the heart (Furnival *et al.* 1970). Because changes in heart rate are known to induce inotropic changes which are

indicated by changes in dP/dt max, the changes in dP/dt max which accompanied the distension of the balloons were examined in experiments in which the heart rate was controlled by electrical pacing of the right atrium. In each of these experiments the heart rate was paced at a rate just above that attained during prior distensions of the balloons, and this controlled rate was maintained throughout each control period and each experimental period. In seven distensions in four dogs the changes in dP/dt max during distension of the balloons at constant heart rate showed an increase of 54 mm Hg/sec (mean; S.D. ± 169; range -138 to $+414$).

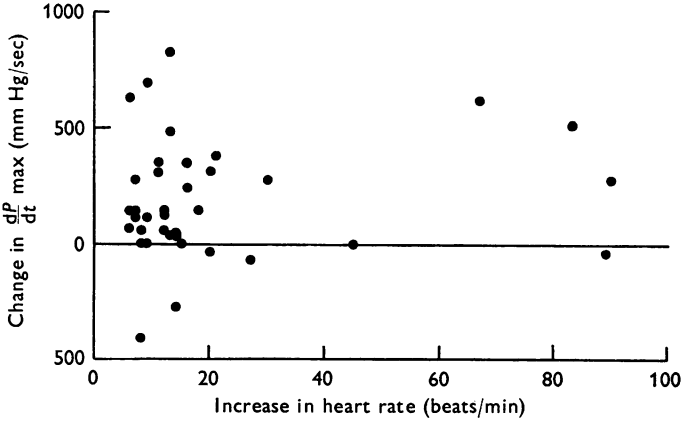

Fig. 2. The relationship between the increase in heart rate and the change in dP/dt max as a result of distending the pulmonary vein/left atrial junctions (thirty-seven observations in twelve dogs). There is no significant correlation between the increases in heart rate and the changes in dP/dt max ($R = 0{\cdot}13$, $0{\cdot}4 < P < 0{\cdot}5$).

dP/dt *max as an index of reflexly induced inotropic changes*

Although previous assessment of the methods used to indicate changes in the inotropic state of the heart had shown that dP/dt max was the most sensitive quantitative index of inotropic changes (Furnival *et al.* 1970), and had shown the technique particularly to be capable of indicating inotropic changes associated with activity in cardio-sympathetic nerves (Furnival, Linden & Snow, 1968*a*), the failure to demonstrate a positive inotropic change during distension of the pulmonary vein/left atrial junctions made it necessary to confirm that dP/dt max could in fact indicate inotropic changes which were induced as a component of a reflex response. A fall in pressure in the carotid sinus brings about reflex changes in the circulation, which are known to include a positive inotropic response of the ventricle (e.g. Sarnoff, Gilmore, Brockman, Mitchell & Linden, 1960*b*; De Geest, Levy & Zieske, 1964). Therefore experiments were per-

formed in which dP/dt max was recorded during occlusion of both carotid arteries; a control record was made, both carotid arteries were occluded and after a second record had been obtained the occlusion of the carotid arteries was released and a second control record was made.

An example of the records obtained before, during and after occlusion of the carotid arteries is shown in Fig. 3; this may be compared with records of distension of the pulmonary vein/left atrial junctions shown in Fig. 1. In Fig. 3, before occlusion of the carotid arteries the control heart

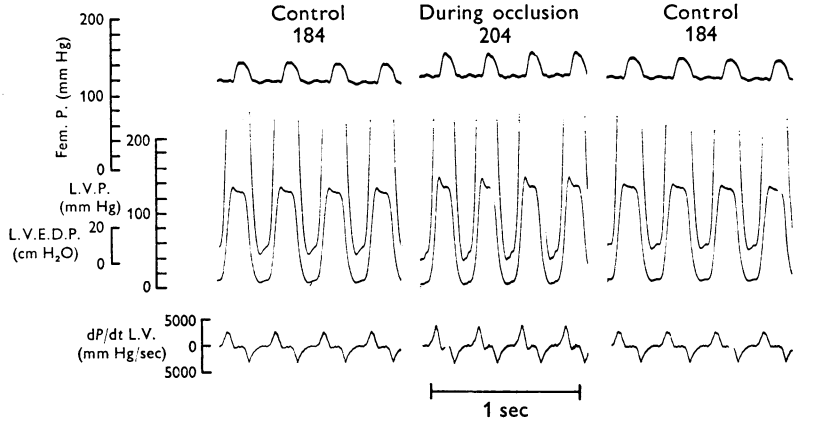

Fig. 3. Records from one dog showing the effect of occluding the carotid arteries. From above downwards Fem. P., pressure in the femoral artery; L.V.E.D.P., end-diastolic pressure in the left ventricle; L.V.P., pressure in the left ventricle; dP/dt L.V., rate of change of pressure in the left ventricle. The number above each panel is the heart rate in beats/min. First panel, control; second panel, during occlusion of the carotid arteries; third panel, 3 min after release of occlusion of the carotid arteries.

rate was 184 beats/min and dP/dt max was 2760 mm Hg/sec; when the carotid arteries were occluded the heart rate rose to 204 beats/min and dP/dt max increased to 3860 mm Hg/sec. The increase in dP/dt max was greater than any increase recorded in all thirty-seven distensions of the pulmonary vein/left atrial junctions described in the twelve dogs. Following release of the clamps on the carotid artery the heart rate fell to 184 beats/min and dP/dt max returned to 2760 mm Hg/sec. The small rise in mean arterial pressure of 9 mm Hg during occlusion of the carotid arteries could not have been completely responsible for the changes in dP/dt max (Furnival *et al.* 1970). In nine other tests in three dogs the mean increase in heart rate was 17·6 beats/min and the mean increase in dP/dt max was 1263 mm Hg/sec. Therefore it appeared that dP/dt max could indicate inotropic changes induced by sympathetic activity which occurred as part of a reflex response.

That these reflex responses in heart rate to distension of balloons at the pulmonary vein/left atrial junctions were the same as those reported previously (Ledsome & Linden, 1964, 1967) involving only efferent sympathetic fibres was shown by sympathetic blockade; section of the ansae subclaviae in six dogs, intravenous injection of propranolol (0·5 mg/kg) in three dogs and/or bretylium tosylate (10 mg/kg) in three dogs each abolished the reflex increase in heart rate.

DISCUSSION

The heart rate response to left atrial distension

Daly & Verney (1927) and Daly, Ludany, Todd & Verney (1937) reported that distension of the left side of the heart caused bradycardia and hypotension. Since then bradycardia has been assumed to be a characteristic response to distension of the left side of the heart (see reviews: Aviado & Schmidt, 1955; Heymans & Neil, 1958). Aviado & Schmidt (1959) failed to produce any changes in heart rate by distension of the left atrium alone and attributed this bradycardia solely to the distension of the left ventricle. No response to distortion of the heart walls or great veins was observed by Klussman, Van Citters & Rushmer (1960).

However, Ledsome & Linden (1964) showed that distension of small balloons placed in the pulmonary vein/left atrial junctions of the anaesthetized dog caused a reflex increase in heart rate. Later, Ledsome & Linden (1967) showed that the distension of a pouch of the left atrium resulted in the same reflex response of an increase in heart rate. Kidd *et al.* (1966) by recording action potentials in the vagi and distending small balloons in the pulmonary vein/left atrial junctions in one series of experiments and distending a pouch in another series of experiments showed that the most likely receptors to be involved in this reflex were those situated in the endocardium of this part of the left atrium; these receptors have been described in the dog by Coleridge, Hemingway, Holmes & Linden (1957). The afferent pathway of this reflex was shown to be in the vagi and the efferent pathway solely in the sympathetic nerves (Ledsome & Linden, 1964, 1967). Karim, Kidd, Malpus & Penna (1971) by recording action potentials in sympathetic efferent nerves in the right ansa subclavia have recently provided direct evidence that stimulation of the left atrial receptors results in an increase in the activity of the efferent sympathetic nerves to the heart.

Since the first demonstration of this reflex in 1964 several other series of experiments have been completed in these laboratories in which this reflex has been demonstrated (Ledsome & Linden, 1968; Carswell, Hainsworth

& Ledsome, 1970; Ledsome & Hainsworth, 1970; Harry, Kappagoda, Linden & Snow, 1970; Karim *et al.* 1971). Including the present investigation where thirty-seven inflations in twelve dogs gave a mean increase in heart rate of 21 beats/min the published investigations contain a total of 310 distensions in 109 dogs with an average increase in heart rate of 23·5 beats/min (range 2–90). It seems reasonable to conclude that in the anaesthetized dog a reflex increase in heart rate can be obtained by stimulation of receptors at the pulmonary vein/left atrial junctions; that the afferent pathway is in the vagi and the efferent is solely in the sympathetic nerves to the heart. It is notable that there is no vagal efferent component to this reflex; no decrease in heart rate and no change in heart rate after section of the ansae subclaviae or administration of a sympathetic β-receptor antagonist (propranolol) have ever been observed. Also, in the experiments of Harry *et al.* (1970) the response to stimulation of left atrial receptors showed no evidence of bradycardia even though the tachycardia of the reflex response had been abolished by acidaemia; acidaemia is known to enhance the effect of increased activity in the vagal nerves to the heart (Campbell, 1955; Linden & Norman, 1969).

It is therefore surprising that Edis, Donald & Shepherd (1970) claim to have observed, during stimulation of left atrial receptors, a reflex hypotension and either tachycardia or bradycardia depending on the heart rate before distension; the efferent limb of their response was said to be in both the vagus nerves and the sympathetic nerves.

These results are obviously different from those obtained in this laboratory following stimulation of left atrial receptors. Although they claim that the difference in response is explained by the removal of baroreceptor activity in their preparation they do not offer an explanation of the findings of Carswell *et al.* (1970) who reported that distension of the pulmonary vein/left atrial junctions with a small balloon in the manner of this laboratory always caused an increase in heart rate although the initial heart rate was varied by controlled carotid artery perfusion over a range of 54–207 beats/min. In other series of investigations in this laboratory increases in heart rate have always been observed in response to stimulation of left atrial receptors even though the initial control heart rate was high, in one instance as high as 220 beats/min; and at this high heart rate there would be little baroreceptor influence to remove.

The fact that they used a balloon 5 times as large as used in this laboratory suggests that the most likely explanation, if indeed a reflex has been demonstrated, is that they are stimulating receptors other than the left atrial receptors. It is not reasonable to assume, as Edis *et al.* (1970) have done, that, because Kidd *et al.* (1966) stimulated only left atrial receptors using small balloons 0·3 cm long, only the left atrial receptors will be

stimulated by the distension of larger balloons 1·5 cm long. Other receptors and nervous structures exist in this area.

Edis *et al.* (1970) in three dogs also created a pouch of the whole left atrium which they perfused at different pressures. No response of an increase in heart rate was observed, only a decrease in peripheral resistance. It is difficult to accept, without evidence, their suggestion of destruction of nerves to the left atrium by an aortic clamp as an explanation of the failure to observe an increase in heart rate; simple stimulation of the ansae subclaviae would have proved this important point.

There is no evidence in their paper that any observed increase in heart rate was a result of an increased sympathetic activity, e.g. they did not attempt to obtain the response after section of the ansae subclaviae, and propranolol in four of the six dogs of their investigation did not alter the response of the increase in heart rate. In fact in the other two dogs atropine was given and this also did not affect the response of slowing of the heart. Giving both propranolol and atropine abolished all the responses to balloon distension but resulted in an initial control heart rate of 147 beats/min. However, regression analysis of all their results obtained before giving both propranolol and atropine (their Fig. 4) gave an intercept on the line of no change in heart rate at an initial heart rate of 145 beats/min; from these results at least one conclusion could be that there is no evidence of nervous involvement in their response at all.

The most charitable conclusion about the investigation of Edis *et al.* (1970) is that the responses they observed were not a result of the stimulation of atrial receptors but were the result of the stimulation of some other receptors. This opinion is supported by the recent preliminary report of Öberg & Thorén (1970) who observed, during rapid haemorrhage in the cat, first an increase in heart rate and then a decrease; atrial receptor discharge fell throughout the haemorrhage. But as the heart rate slowed there was a concomitant increase in the impulse traffic in other vagal afferent fibres, said to be non-myelinated, which, prior to the slowing, had shown only minimum activity and no cardiac rhythm either in the control period or during haemorrhage. Slowing of the heart rate was observed by Edis *et al.* (1970) under conditions similar to those of Öberg & Thorén (1970); there was a fast heart rate (> 200 beats/min) with minimum baroreceptor stimulation and maximum sympathetic effect on the heart.

Reflexes involving cardiac sympathetic nerves: inotropic changes

From many investigations involving stimulation of the sympathetic nerves to the heart, e.g. Rohse & Randall (1955), Anzola & Rushmer (1956), Sarnoff *et al.* (1960*a*), Levy, Ng & Zieske (1966), it is known that as well as an increase in heart rate there is a concomitant positive inotropic

response of the ventricles. Again the examination of reflex responses involving efferent sympathetic nerves to the heart, e.g. the effect of a fall in pressure in the carotid sinus (e.g. Sarnoff *et al.* 1960*b*), has shown not only an increase in heart rate but also a positive inotropic response. Therefore it was expected that the reflex first shown by Ledsome & Linden (1964), in which the left atrial receptors were stimulated and the reflex response completely abolished by sympathetic blockade or by section of the ansae subclaviae, would involve a positive inotropic response. In addition in some of the experiments in the previous investigations (e.g. Ledsome & Linden, 1964) there were small increases in blood pressure which could suggest that there had been an increase in cardiac output possibly resulting from a positive inotropic response.

The present investigation sought to establish a positive inotropic response as part of the reflex involving the left atrial receptors; in the event no inotropic response was observed. The technique of recording the maximum rate of change of pressure in the left ventricle (dP/dt max) and of using this as a sensitive quantitative index of a change in the inotropic state of the left ventricle has previously been reported (Furnival *et al.* 1970). In the present investigation it has also been demonstrated that this technique was sensitive enough to recognize the positive inotropic response of the left ventricle which results from occlusion of the carotid arteries and the consequent fall in pressure in the carotid sinuses. However, in thirty-seven distensions of the pulmonary vein/left atrial junctions in the twelve dogs of this investigation there was a mean increase in heart rate of 21 beats/min but only a small increase of 193 mm Hg/sec in dP/dt max; this evidence allows only the conclusion that there is no significant concomitant positive inotropic response. This conclusion from the over-all results is emphasized if attention is paid to the dog in which the greatest increase in heart rate was observed in response to the distension of pulmonary vein/left atrial junctions; in this dog there was an increase of 90 beats/min superimposed on the control heart rate of 123 beats/min and yet the increase in dP/dt max was only 276 mm Hg/sec.

It could be argued that this surprisingly small increase in dP/dt max results in part from a withdrawal of activity in the sympathetic nerves to the heart muscle, which in turn results from an increase in the stimulation of arterial baroreceptors because of the increased heart rate at a constant mean arterial blood pressure. Some evidence to support this hypothesis may be derived from the observation in the denervated heart that a similar increase in heart rate brought about by electrical pacing of the atrium caused a positive inotropic effect (Furnival *et al.* 1970) which was greater than that observed during distension of the balloons in the pulmonary vein/left atrial junctions. However in the experiments in which the heart

rate was controlled and maintained constant during the distension of the balloons, the increase in dP/dt max was smaller than that observed in those experiments in which the heart rate was allowed to increase. This evidence suggests that the most important mechanism causing the small increase in dP/dt max during balloon distension is the secondary inotropic effect of the increase in heart rate, i.e. the 'Bowditch staircase effect' (Bowditch, 1871), and that whereas withdrawal of activity in the sympathetic nerves as a result of increased stimulation of arterial baroreceptors may be a possible explanation of the small magnitude of the change in dP/dt max when the heart rate was allowed to increase, it could not be offered as an explanation in those experiments in which the heart rate was held constant. Thus the inotropic response which results directly from stimulation of the left atrial receptors is negligible.

The fact that only small and variable changes in blood pressure were observed to accompany the reflex increase in heart rate also suggests that there is no concomitant positive inotropic response.

Thus it may be concluded that stimulation of left atrial receptors results in a reflex increase in activity in sympathetic nerves involving an increase in the heart rate but not accompanied by a positive inotropic response; that is, the reflex involves only those sympathetic nerves in the ansae subclaviae which innervate the sinu-atrial node.

Differentiation in the organization of sympathetic nerves

The observation that this reflex response on the heart is confined to the sympathetic nerves to the sinu-atrial node and does not affect the ventricular muscle is significant not only to the control systems involved in controlling the function of the heart but also in relation to sympathetic activity in general. Earlier in this century Cannon (1932) regarded the sympathetic nervous system and the adrenal medulla as an integrated unit which when activated caused widespread changes throughout the body and made significant contributions to homoeostasis. Cannon (1932) considered that all the viscera were influenced simultaneously in one direction or the other by increases or decreases in the tonic activity of the sympathetic division. It is generally accepted that there is a tendency for the sympathetic system on occasion to act as a whole, e.g. in haemorrhage, but deviations from this theme are all known; the sympathetic nerves of smooth muscle in the gut, eye and bronchi are capable of being activated independently.

It has been suggested also by Daly & Scott (1962), after experiments in which the chemoreceptors were stimulated, that there is some differentiation of the organization of sympathetic efferent nerves to the cardiovascular system. Daly & Scott (1962) in experiments in which respiration was

controlled showed that stimulation of the carotid bodies resulted in a decrease in heart rate and that part of this response resulted from a withdrawal of sympathetic activity; at the same time they observed an increase in sympathetic activity to the systemic arterioles. Also Daly & Daly (1959) observed that chemoreceptor stimulation caused pulmonary vasoconstriction which was mediated through the stellate ganglia. These results suggest that with regard to the carotid body reflex there is differentiation of the organization of sympathetic nerves controlling heart rate on the one hand and peripheral and pulmonary vascular resistance on the other. The present investigation provides evidence that the sympathetic nerves to one part of the cardiovascular system (the sinu-atrial node) are capable of a discrete response. This point of view is further supported by the evidence obtained by Karim *et al.* (1971), who, by recording action potentials in efferent sympathetic nerve fibres, demonstrated that stimulation of left atrial receptors resulted in an increase in activity in the cardiac nerves, a decrease in activity in the renal nerves and no change in activity in the abdominal nerves.

The Bainbridge reflex

It has been suggested that in the cardiovascular system all of the 'Cardiovascular reflexes which have been well studied either slow the heart or lower the blood pressure, or do both in response to an increase in pressure in, or stretch of the appropriate vessels; this generalization requires the rejection of the Bainbridge reflex ...' (Widdicombe, 1964); similar opinions have been expressed by Aviado & Schmidt (1955).

The reflex increase in heart rate obtained by stretching the left atrial receptors (first described by Ledsome & Linden, 1964) refutes this general statement. Possibly, the response of an increase in heart rate alone from stimulation of the left atrial receptors, together with the preliminary report (Kappagoda, Linden & Snow, 1970) that stimulation of right atrial receptors results in a similar reflex response of an increase in heart rate, will re-install the Bainbridge reflex, though not in its original form.

Other reflex responses to left atrial distension

Other investigations have shown that stimulation of the left atrial receptors in a similar manner by distension of small balloons in the pulmonary vein/left atrial junctions results in no change in respiration (Ledsome & Hainsworth, 1970), and in no change in peripheral vascular resistance (Carswell *et al.* 1970).

However, stimulation of left atrial receptors causes an increase in urine flow (Ledsome & Linden, 1968) similar to that caused by a rise in left atrial pressure resulting from obstruction of the mitral orifice (Ledsome, Linden

& O'Connor, 1961). This diuresis is known to be dependent on the integrity of the afferent nerves from the left atrial receptors (Ledsome & Linden, 1968) but not on the integrity of the ansae subclaviae or the nerves to the kidney (Ledsome *et al.* 1961; Carswell, Hainsworth & Ledsome, 1968). The blood borne agent responsible for the diuresis was thought not to be the antidiuretic hormone because the response was obtained in the presence of an infusion of vasopressin sufficient to maintain a high concentration in the circulating blood (Ledsome *et al.* 1961). However, in a recent preliminary report Ledsome & Mason (1970) obtained a similar increase in urine flow by reducing a high concentration of vasopressin in the circulating blood, to a lower but still high concentration, which suggests that the antidiuretic hormone could, nevertheless, be the agent involved in the diuresis observed to result from the stimulation of left atrial receptors. Also, Karim *et al.* (1971), in a preliminary report, have demonstrated a hitherto unrecognized efferent limb of this reflex in the sympathetic nerves to the kidney. Karim *et al.* (1971) observed a decrease in activity in sympathetic nerves to the kidney during the inflation of small balloons at the pulmonary vein/left atrial junctions. Therefore it is possible that the diuresis observed in the innervated kidney in response to the stimulation of left atrial receptors is partly nervous in origin.

Thus, in summary, stimulation of left atrial receptors causes an increase in activity in sympathetic nerves to the sinu-atrial node resulting in an increase in heart rate, a decrease in activity in sympathetic nerves to the kidney with unknown effects and a diuresis probably caused by a reduction in the concentration of antidiuretic hormone in the circulating blood. Also stimulation of the right atrial receptors results in the same reflex response in heart rate; it is not known yet whether effects on the kidney similar to those resulting from stimulating left atrial receptors will be observed.

However, this reflex response of an increase in heart rate from left and right atrial receptors has only been observed in anaesthetized dogs and its function in the intact animal is unknown. It is known that a simple increase in heart rate (e.g. produced by electrical pacing) over the normal range of function (70–190 beats/min) reduces the cardiac output slightly and that this results in a decrease in both end-diastolic volume and stroke volume (Linden, 1963, 1968). Therefore it is possible to speculate that the importance of the reflex may be that it represents one of the mechanisms which regulate the size of the heart to within very narrow limits, first by its effect on the heart rate and secondly by its effect on the kidney and the volume of extracellular fluid. Because (1) the duration of ventricular systole and thus the time of filling of the atrium during this period is relatively constant, and (2) the receptors respond to a rate of change of

deformation during this period as well as an increase in mean pressure, it is suggested that this reflex, by increasing the heart rate in response to an increased rate of inflow into the atrium during ventricular systole, maintains the volumes of the heart relatively constant during the increased flow of blood through the heart, i.e. during the increased venous return. Thus an increased inflow into the left atrium would cause an increased rate of change of pressure in the atria during ventricular systole, an increased rate of discharge of the atrial receptors, and an increased heart rate: this increase in heart rate would reduce the time of filling and maintain the end-diastolic volume relatively constant despite the increase in venous return.

Such a mechanism operating in response to an increased inflow to the heart and causing an increase in heart rate would allow the heart to work over a restricted range of volumes with smaller end-diastolic volumes and smaller stroke volumes than would otherwise be attained; this explanation is similar to that made for the function of the Bainbridge reflex by Anrep & Segall (1926) who suggested that the effect of an increase in heart rate would be to minimize the increase in stroke volume which would otherwise occur from large intravenous infusions. A corollary of this speculation is that such a reflex increase in rate combined with the other mechanisms determining stroke volume (the Starling mechanism and increased activity in the sympathetic nerves) would extend the upper limit of obtainable cardiac output in exercise as suggested by Linden (1968). The almost linear relationship between heart rate and cardiac output which has been observed during exercise suggests the existence of a control mechanism relating heart rate to the increase in venous return; it is at least possible that this reflex will form the basis of the required control mechanism (Linden, 1965).

Also it is possible to speculate that this reflex mechanism maintains the heart size within narrow limits not only in the face of increased venous return but during an increase in blood volume. An increase in blood volume results in an increase in mean atrial pressure which in turn causes an increased discharge from atrial receptors. In the short term the resulting increase in heart rate would prevent an increase in heart volumes and in the long term the mechanisms involving the kidney may adjust the extracellular fluid volume so that the blood volume, and therefore heart volumes, are less.

Therefore it is concluded that it is a reasonable speculation that the atrial receptors are the first link in a negative feed-back mechanism controlling heart volumes.

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