J. Physiol. (1978), **280**, *pp.* 303–317
With 9 text-figures
Printed in Great Britain

TYPE A ATRIAL RECEPTORS IN THE CAT: EFFECTS OF CHANGES IN ATRIAL VOLUME AND CONTRACTILITY

BY GIORGIO M. RECORDATI

From the Istituto Ricerche Cardiovascolari, University of Milan, and Centro Ricerche Cardiovascolari, C.N.R., Via F. Sforza 35, 20122 Milan, Italy

(*Received 27 July 1977*)

SUMMARY

1. Action potentials were recorded from filaments of the right cervical vagus in anaesthetized, paralysed cats. Right atrial receptors with type A (twelve units) and Intermediate type (two units) patterns of spontaneous discharge were selected and their responses to changes in atrial volume were analysed.

2. Changes in atrial volume of similar magnitude were produced under four different conditions: *a*, innervated hearts; *b*, denervated hearts; *c*, depression of atrial muscle contractility induced after cardiac denervation and *d*, non-beating hearts.

3. In innervated hearts the systolic discharge of each receptor showed a characteristic response to changes in atrial volume. Cardiac denervation and depression of atrial contractility markedly altered this response in terms of frequency of discharge, threshold and 'sensitivity'.

4. During increments in atrial volume all the receptors but one assumed an Intermediate pattern of discharge. The diastolic firing rate was, however, higher for any given atrial pressure, in innervated hearts than under conditions *b*, *c* and *d*.

5. In innervated hearts the response of the receptors to atrial systole was characterized by a higher frequency of discharge and a lower threshold with respect to the responses of the same receptors to atrial filling. These differences were minimized at high atrial volumes and during depression of atrial contractility.

6. The results indicate that the responses of the receptors to atrial systole are mainly dependent upon the state of contraction of atrial muscle and that the differences between systolic and diastolic discharge are mainly due to the high dynamic component of the stretch during atrial contraction.

INTRODUCTION

It has been recently demonstrated that the systolic discharge of type A and Intermediate type atrial receptors is dependent upon the active tension developed by atrial muscle during contraction (Recordati, Lombardi, Bishop & Malliani, 1976). Few and contradictory results have emerged from studies of the response of these receptor types to changes in atrial volume. For example, it has been reported recently that, in the beating heart, atrial volume changes do not affect (Arndt, Brambring, Hindorf & Röhnelt, 1971) or decrease (Hakumaki, 1970) the systolic discharge of type A atrial receptors, while in the non-beating heart increments in atrial volume have

been shown to produce an increase in receptor activity (Arndt, Brambring, Hindorf & Röhnelt, 1974).

The present experiments were undertaken to elucidate the effects of changes in atrial volume and the interactions of changes in atrial volume and contractility on type A receptor discharge. The results indicate that the responses of the receptors to changes in atrial volume in terms of frequency of discharge, threshold and sensitivity are markedly dependent upon the contractile state of atrial muscle.

It is known that during increments in atrial volume, type A receptors also become active during atrial filling (Neil & Joels, 1961). Their response to atrial contraction (active stretch of atrial muscle) is characterized by a higher frequency of discharge and a lower threshold than the response to atrial filling (passive stretch of atrial muscle) (Recordati *et al.* 1976). Thus a second purpose of the present study was to investigate the source of these differences, comparing the responses of the same receptors to atrial contraction and filling at different atrial pressures and contractile states. It has been found that the differences in the responses to active and passive stretch might be explained on the basis of the high dynamic component of the stimulus which excites receptor endings during atrial contraction.

A preliminary account of this work has been presented (Recordati, 1976).

METHODS

The results were obtained from fourteen experiments on cats (2·4–4·0 kg) anaesthetized by I.P. injection of sodium pentobarbitone (35 mg/kg). The trachea was cannulated and each animal was artificially ventilated after I.V. injection of gallamine triethiodide (3 mg/kg; Sincurarina, Farmitalia). The respirator was adjusted to maintain arterial P_{O_2}, P_{CO_2} and pH within normal limits. Polyethylene catheters were inserted into (1) a femoral artery, (2) the right atrium through the external jugular vein and (3) a femoral vein. Right atrial and femoral arterial pressures were measured with Statham P23De strain gauges. The frequency responses of the catheter–manometer systems were flat (±5%) to 30 Hz. In all animals the chest was opened bilaterally from the second to the fifth intercostal space and the sternum was removed. The left thoracic vagus was dissected from the surrounding tissues. In nine experiments the left thoracic vagus was cut centrally, and propranolol (0·5 mg/kg; Inderal, I.C.I.) was injected I.V. The peripheral cut end of the left thoracic vagus was stimulated electrically (Grass S4 stimulator) with rectangular pulses (5–10 V, 3 msec) at frequencies of 10–20 Hz, and acetylcholine bromide (1–10 μg/kg; Pragmolina, Farmitalia) was injected. In three experiments the heart was surgically denervated by bilateral vagotomy and removal of the stellate ganglia. After denervation isoprenaline (0·2 μg/kg; Alupent, Boehringer) and acetylcholine were injected I.V.

Afferent nervous activity was recorded as previously described (Recordati, Lombardi, Bishop & Malliani, 1975) from filaments isolated under a dissecting microscope from the right cervical vagus. Right atrial and femoral arterial pressures, e.c.g. (Grass P511 preamplifier), tracheal pressure, nervous impulses and instantaneous frequency of nervous discharge were recorded with a multichannel optical recorder (Hewlett-Packard 4578A) and on a magnetic tape recorder (HP 3907C).

Analysis of neural activity. Analysis of neural activity was restricted to the expiratory phase of the respiratory cycle. The following were calculated: (i) the number of spikes (n) in the systolic and diastolic trains of impulses per cardiac cycle; (ii) the duration of both trains of impulses (d.b.); (iii) the mean frequency of discharge in each burst ($n-1$/d.b.); and (iv) the peak frequency of discharge in the systolic (p.f.s.) and diastolic (p.f.d.) bursts. The interspike intervals were measured by a digital neural spike analyser with an accuracy within 1%. The analogue output level of the analyser was proportional to the pulse interval and was displayed with a delay of one interspike interval (Fig. 1) (Recordati *et al.*, 1976). The p.f.s. and the mean frequency of discharge in the systolic burst were correlated to the pressure at the foot of the 'a' wave of right atrial pressure (initial systolic atrial pressure = $P_{i,s}$), to the pressure at the peak

of the 'a' wave (peak systolic atrial pressure = $P_{max.,s}$), and to the amplitude of the 'a' wave ($P_{max.}$–$P_{l,s}$ = ΔP). The p.f.d. and the mean frequency of discharge in the diastolic burst were correlated to the pressure at the peak of the 'v' wave of atrial pressure tracing ($P_{max.}$). Data were collected from animals having systolic blood pressure above 100 mm Hg.

Experimental protocol. The nerve impulses initiated by the activation of the receptors were recorded during changes in blood volume caused by withdrawal of 30–50 ml. blood (approximately 10 ml./min) and by infusion of 40 ml. warm saline (10 ml./min) under four different conditions. Condition *a*: changes in atrial volume were made while the left vagus was still intact and before I.V. administration of propranolol (eleven units); the heart was innervated, with the exception of the right vagus, which was cut centrally at the beginning of each experiment. Condition *b*: changes in atrial volume followed sectioning of the left vagus in the thorax and propranolol infusion (nine units). Condition *c*: changes in atrial volume were induced after cardiac denervation and were accompanied by either efferent vagal stimulation (five units) or ACh infusion (four units). Condition *d*: in five experiments the recording of the nervous activity was continued after the animals had been killed by bleeding and asphyxia, and the responses of five receptors to slow changes in atrial volume were then studied in the non-beating heart (Recordati *et al.* 1975). Changes in atrial volume during each condition were initiated after the animal was allowed to recover from previous interventions (30–60 min).

Location of the receptors. To ascertain that all the receptors studied were located in the right atrium, the manoeuvres suggested by Paintal (1973) were used. In addition, at the end of each experiment the location of the receptor was determined by probing the internal and external surfaces of the right atrium in the opened heart (Coleridge, Hemingway, Holmes and Linden, 1957). Nine receptors were located at the junction of the superior vena cava with the right atrium (one of these, above the azygos vein), three at the junction of the inferior vena cava and two on the lateral free wall of the right atrium. Experiments in which the receptor could not be precisely located were disregarded.

Terminology and definitions. The dynamic events occurring during the atrial cycle have been described by the conventional cardiovascular terminology, and, in addition, in terms of muscle mechanics (Recordati, Lombardi, Malliani & Brown, 1974). Hence:

atrial systole = active stretch of atrial muscle,

atrial diastole = passive stretch of atrial muscle,

changes in atrial volume = changes in initial level or amount of stretch = changes in the static component of stretch,

changes in atrial contractility = changes in the rate of pressure development and wall movement = changes in the dynamic component of stretch,

'*sensitivity*' of a receptor to pressure changes has been defined as the slope of the relationships between firing rate and pressure. The ratio between two variables is the slope of the relationships. Hence the ratio of the p.f.s. to ΔP was used to describe the 'sensitivity' of the systolic discharge to the amplitude of the 'a' wave of atrial pressure.

RESULTS

Eleven cats were used to study the responses to changes in atrial pressure and volume of eleven right atrial receptors which were spontaneously active during atrial systole. Fig. 1 shows an example of the data on which the results are based. Under control conditions and at low atrial pressure (Fig. 1*A*), all but two of the receptors were spontaneously active only during atrial systole; the exceptions were two intermediate-type receptors (indicated in all the Figures by symbols ◇ and ▼) which were spontaneously active during atrial filling as well as with a very low frequency of discharge. When atrial pressure was increased by infusion of saline (Fig. 1 *B*, *C*) all the receptors but one (which was located above the junction of the azygos vein with the superior vena cava and indicated in the Figures by symbol □) also became active during atrial filling. The responses of each receptor to atrial contraction and to filling differ, however, in threshold (in Fig. 1*A* the receptor is active only during atrial

systole), in firing rate and in their modulation by pressure and volume changes. In fact, while the p.f.s. decreased from Fig. 1*B* to 1*C*, the p.f.d. progressively increased.

The following results stem from the analyses of the responses of the receptors to active and passive stretch of atrial muscle during changes in atrial volume performed under the four conditions *a*, *b*, *c* and *d*.

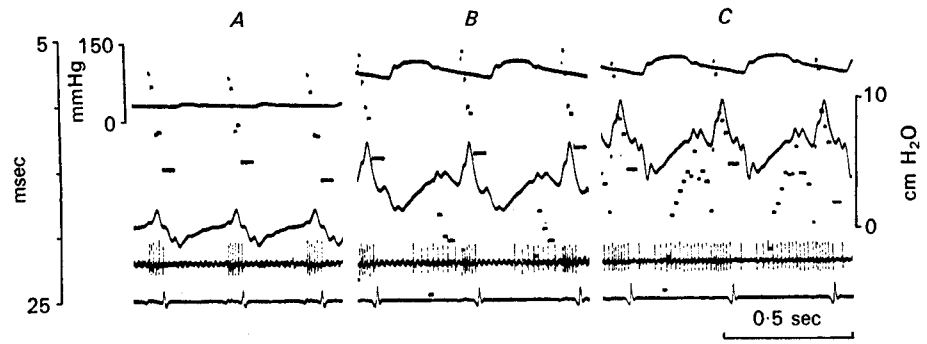

Fig. 1. Effects of haemorrhage and infusion of saline on the activity of a type A right atrial receptor whose receptive field was at the junction of the superior vena cava with the right atrium. Tracings in *A*, *B* and *C* represent, from top to bottom, the femoral blood pressure, right atrial pressure, record of action potentials and e.c.g. Dots and broken lines are the analogue output of the digital neural spike analyser. The level of each of them corresponds to the length of the preceding interspike interval (calibration at the left-hand side: 5–25 msec). The reading of the last interspike interval of the burst persists for the pre-set range of reading (50 msec). Interspike intervals longer than 25 msec are off scale. During the initial control period this receptor showed a burst of impulses synchronous with the 'a' wave of atrial pressure. *A*, end of haemorrhage; the receptor is still active only during atrial systole. *B*, after reinjection of the blood and additional 10 ml. saline I.V.; the unit assumed an Intermediate pattern of discharge, being active during both atrial filling and contraction. *C*, after injection of additional 30 ml. saline I.V.; the diastolic discharge increased with respect to *B*, while the systolic one decreased. This receptive unit is indicated in all the following Figures by the symbol △.

Systolic discharge

I. Response to volume changes as a function of initial and peak systolic pressures

The receptors' responses to atrial contraction were evaluated by relating both the peak frequency and the mean frequency of systolic discharge to $P_{i,s}$ and $P_{max.,s}$. Under control conditions the average p.f.s. was $184{\cdot}3 \pm 28{\cdot}1$ impulses/sec (mean ± S.E.), the average $P_{i,s}$ was $2{\cdot}9 \pm 0{\cdot}4$ cm H_2O, and the average $P_{max.,s}$ was $4{\cdot}9 \pm 0{\cdot}5$ cm H_2O.

Fig. 2*A* displays the relationships between $P_{max.,s}$ and firing rates of eleven receptors during condition *a*. The receptors differed in their responses to increments in atrial pressure which were initiated at the lowest pressure levels occurring at the end of haemorrhage. For example, the three receptors with the lowest spontaneous firing rate (indicated by symbols ×, ◆ and ●) and two other receptors (◇ and □) modified their discharge only slightly. The two receptors with the highest spontaneous firing rate (▽ and ▲) and another one (△) decreased their impulse frequencies for increments in $P_{max.,s}$ above 6 cm H_2O. The firing rate of two other receptors (○

and ■) was higher at the end of bleeding than under control conditions (the control values of $P_{max.,s}$ were 4·2 and 4·8 cm H_2O respectively).

Under condition *a*, withdrawal of blood always produced an increase in heart rate, due to the activation of baroreceptor reflexes. It has been previously demonstrated that heart rate changes *per se* do not affect the systolic discharge of these receptors which, conversely, could always be activated by efferent sympathetic stimulation (Recordati *et al.* 1976). Heart rate changes indicate, however, that alterations in the sympathetic outflow to the heart may alter the responses to blood volume changes.

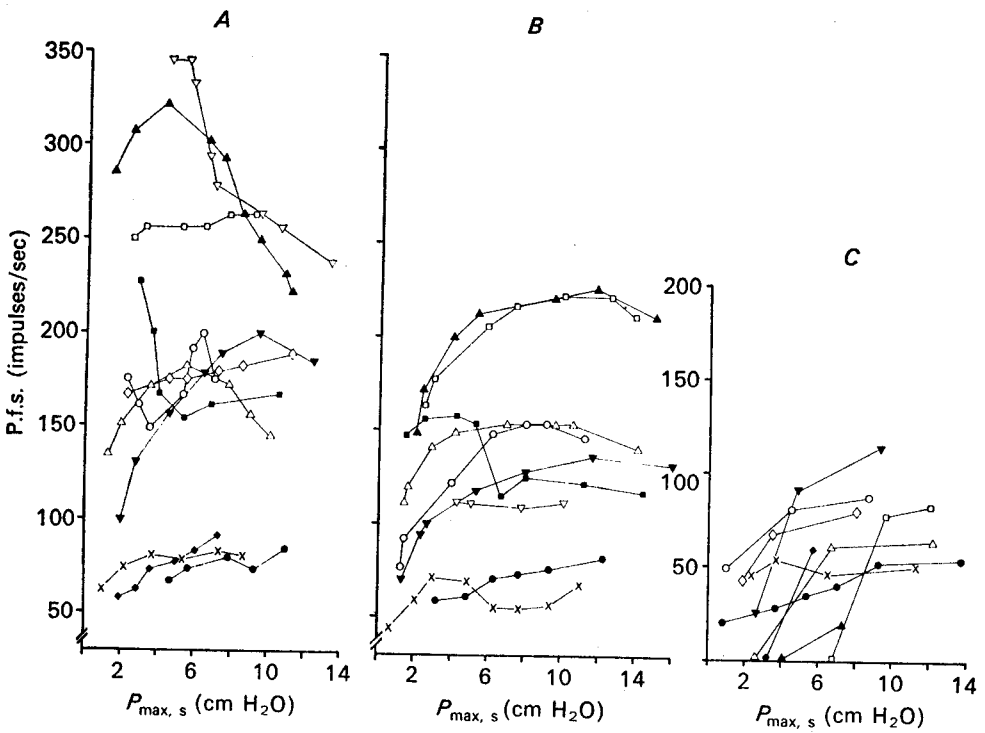

Fig. 2. Relationships between peak frequency of discharge in the systolic train of impulses (p.f.s.) and peak systolic atrial pressure (peak of the 'a' wave, $P_{max.,s}$) during changes in atrial volume. *A*, eleven receptors studied in innervated hearts. *B*, nine receptors studied after cardiac denervation. *C*, nine receptors studied during depression of atrial contractility induced by electrical stimulation of the left vagus and by ACh infusion. In this and following Figures the same symbol has been used to indicate the same receptive unit. Description in the text.

For this reason the responses of nine of these receptors to volume changes were also studied after sectioning of the left vagus in the thorax and I.V. infusion of propranolol (condition *b*). After cardiac denervation (Fig. 2*B*) the systolic firing rate of the receptors was lower than under condition *a* (average p.f.s. 130·8 ± 16·9 impulses/sec) although atrial pressure was slightly increased with respect to control (average $P_{1,s}$ 4·8 ± 0·6 cm H_2O and average $P_{max.,s}$ 6·1 ± 0·6 cm H_2O). Comparing the position of the curves in Fig. 2*A* and *B*, it appears that the decrease in discharge was more pronounced for the receptors which under condition *a* had the highest spontaneous

firing rate. After denervation, moreover, none of the receptors increased their activity during haemorrhage, unlike the increase found in innervated hearts.

Under condition *c*, that is during depression of the contractility of atrial muscle induced by efferent vagal stimulation (five units) or ACh infusion (four units), as shown in Fig. 2*C*, the systolic discharge was even lower than under condition *b* for values of $P_{max.,s}$ ranging from 2 to 10 cm H_2O; four receptors were inactive when it was below 2 cm H_2O. This last finding indicates that the pressure threshold for responses to atrial contraction increased during depression of atrial muscle contractility. Also of note is that, for any given pressure the receptors had more similar firing rates under condition *c* than under condition *a*. Similar results to those shown in Fig. 2 were obtained by relating the peak firing rate to the pressure at the foot of the 'a' wave.

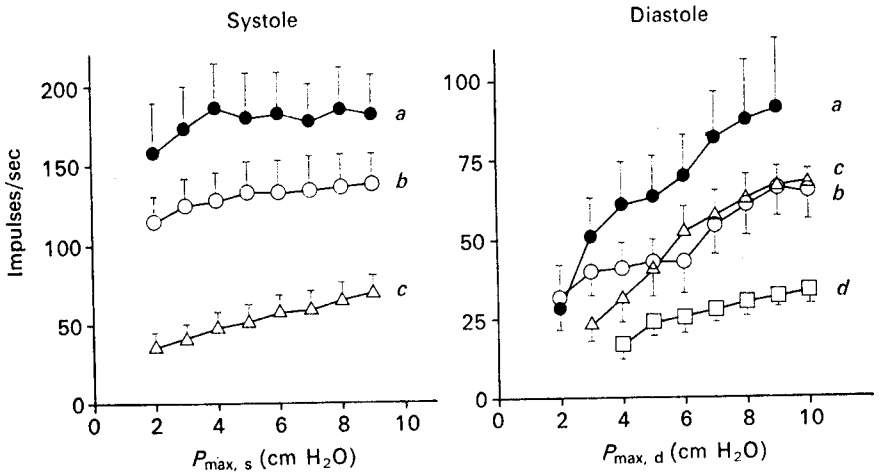

Fig. 3. Effects of alterations of the inotropic state of the heart on the responses of the receptors to changes in atrial pressure. Systole: relationships between average peak systolic firing rate and peak systolic atrial pressure ($P_{max.,s}$; peak of the 'a' wave). Diastole: relationships between average peak diastolic firing rate and peak diastolic atrial pressure ($P_{max.,d}$; peak of the 'v' wave). *a*, innervated hearts; *b*, denervated hearts; *c*, during vagal stimulation and ACh infusion; *d*, non-beating hearts.

Fig. 3 (left, systole) shows the effects of the decrease in inotropic state of the heart on the average peak systolic firing rate of all the receptors studied. The position of the curves was shifted downwards, indicating that for similar pressures the firing rate of the receptors was lower when the inotropic state of the heart was depressed. The decrease in firing rate between condition *a* and *b* (nine units) and between *b* and *c* (seven units) was statistically significant ($P < 0{\cdot}05$, paired *t* test). Depression of atrial contractility also affected the sensitivity of the receptors. These alterations, evident at a visual inspection, were however inconsistent in their direction, some receptors showing an increase and some others a decrease in the slope of the plots.

To verify whether the interruption of efferent sympathetic activity to the heart, and not propranolol itself, was responsible for the decrease in cardiac contractility and hence in receptor discharge, in three experiments (three receptors) cardiac denervation was performed by bilateral vagotomy and surgical removal of the

stellate ganglia (Fig. 4). The systolic discharge (control average peak systolic firing rate 129·5 ± 14·3 impulses/sec; Fig. 4*A*) markedly decreased after sympathectomy (average p.f.s. 62·1 ± 16·4 impulses/sec) and the units also became active during atrial filling (Fig. 4*B*). After surgical denervation it was then possible, by infusing isoprenaline I.V., to induce an increase in cardiac contractility. As shown in Fig. 4*C*, the

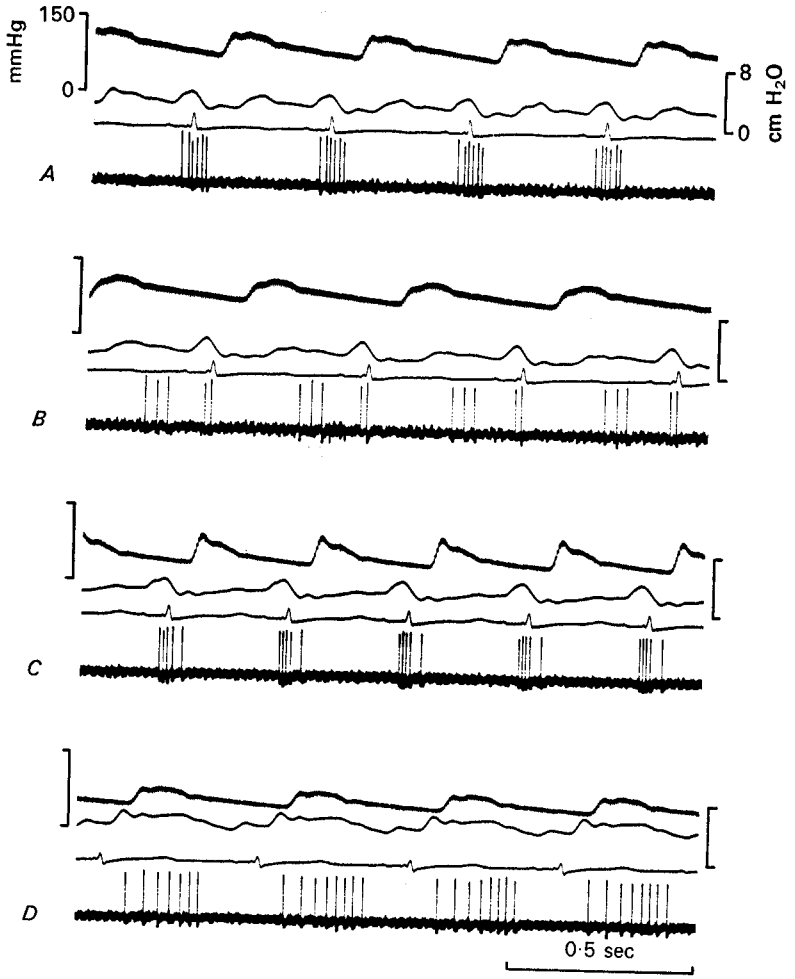

Fig. 4. Responses of a right atrial receptor with a type A pattern of discharge to alterations in cardiac contractility. *A*, control. *B*, after surgical bilateral removal of the stellate ganglia. *C*, during isoprenaline-induced increments in atrial contractility. *D*, during depression of the strength of atrial contraction induced by ACh. Note the conversion into an Intermediate and type B pattern of discharge occurring in *B* and *D* respectively.

receptors resumed their original systolic pattern of discharge and the frequency of firing was even higher than under control conditions. In contrast, when atrial contractility was depressed by an I.V. injection of ACh, the receptors lost their systolic burst and became active only during atrial filling (Fig. 4*D*).

II. Responses to atrial volume changes as a function of the amplitude of the 'a' wave

In conditions *a*, *b* and *c*, changes in atrial volume altered initial and peak systolic pressures and also the amplitude of the 'a' wave ($P_{max.,s} - P_{i,s} = \Delta P$), which can be considered an index of the strength of atrial contraction (Recordati *et al.* 1976). Fig. 5 shows the average changes in ΔP in relation to $P_{i,s}$, for nine experiments and under three different conditions. ΔP was significantly higher under condition *a* ($P < 0{\cdot}01$, paired *t* test, Fig. 5*A*) than under condition *b* at $P_{i,s}$ values ranging from 1 to 6 cm H_2O, and it was significantly higher ($P < 0{\cdot}01$) under condition *b* than under condition *c* at $P_{i,s}$ values ranging from 3 to 8 cm H_2O. This progressive decrease in ΔP reflects the decrease in the strength of atrial contraction over these three ranges of conditions and explains why the frequency of the systolic discharge was lower under conditions *b* and *c* than under condition *a*.

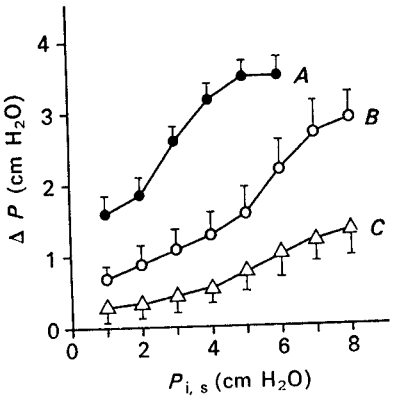

Fig. 5

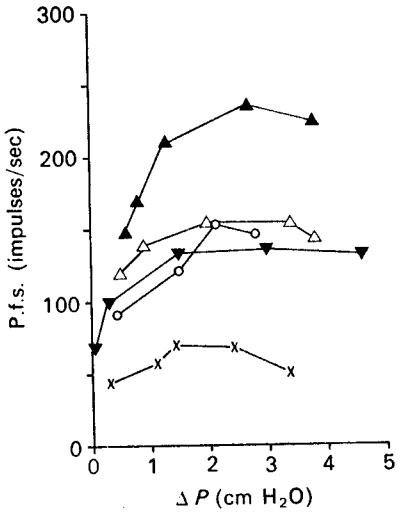

Fig. 6

Fig. 5. Relationships between amplitude of the 'a' wave (ΔP) and initial systolic atrial pressure ($P_{i,s}$) during changes in atrial volume. Average data from nine experiments. *A*, innervated hearts. *B*, denervated hearts. *C*, during vagal stimulation and ACh infusion.

Fig. 6. Relationships between peak frequency of discharge in systolic train of impulses and amplitude of the 'a' wave (ΔP) for five receptors studied in denervated hearts. Increments in ΔP above 2·5 cm H_2O were not accompanied by further increase in systolic firing rate.

Fig. 5 also indicates that under condition *a*, *b* or *c* the ΔP may be altered by changes in atrial volume. Accordingly, to evaluate the receptors' responses to alterations in the strength of contraction due to changes in atrial volume, the relationships between receptor discharge and ΔP have been studied. Only condition *b* was employed, to avoid reflex alterations in cardiac contractility. Fig. 6 shows these relations for five receptors. It can be seen that when the amplitude of the 'a' wave was above 2·5 cm H_2O, none of the receptors increased its firing rate, although further increments in

atrial pressure produced further increases in ΔP. Similar results were obtained for all nine receptors studied under condition *b*. That this indifference to increments in ΔP at high atrial pressure was due to saturation of the receptor discharge is unlikely, since under condition *a* the receptors were able to discharge at a higher frequency. These results show that in a given contractile state the 'sensitivity' of the receptors to ΔP (i.e. the slope of the relationships between the p.f.s. and ΔP) is greater at low than at high atrial pressures and that it decreases with increasing atrial volume.

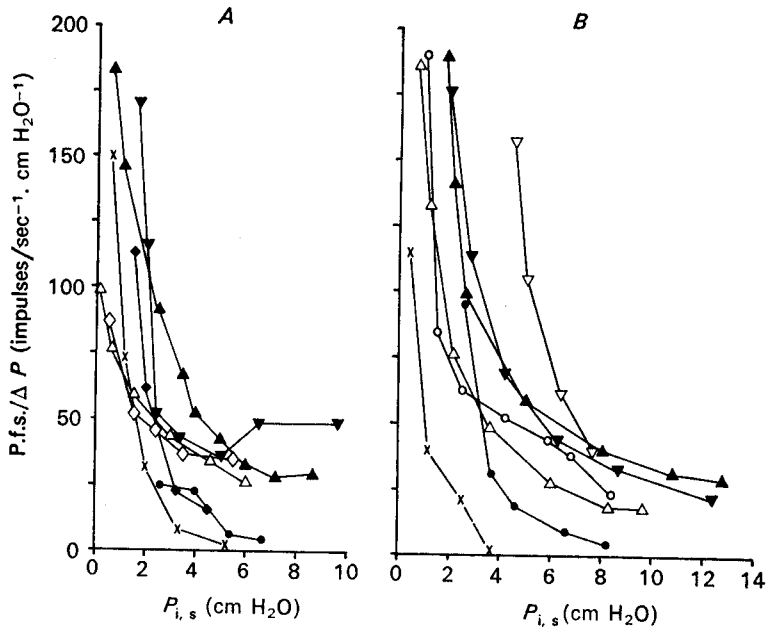

Fig. 7. Relationships between 'sensitivity' of the systolic discharge to amplitude of the 'a' wave (ratio between p.f.s. and ΔP) and initial systolic atrial pressure ($P_{i,s}$ during changes in atrial volume. *A*, seven receptors studied in innervated hearts. *B*, seven receptors studied after cardiac denervation. Increments in $P_{i,s}$ were accompanied by marked decrease in 'sensitivity' to amplitude of the 'a' wave.

These responses of type A atrial receptors closely resemble the responses of Golgi tendon organs (the 'in series' muscle receptors) to changes in muscle length (Stephens, Reinking & Stuart, 1975). To reveal the extent of this similarity an analytical approach was employed that has been recently applied to tendon organs. The ratio between peak systolic firing rate and amplitude of the 'a' wave (p.f.s./ΔP = slope of the relationships between the two variables) was plotted against the changes in $P_{1,s}$ produced by volume loading under conditions *a* and *b*. As shown in Fig. 7, the slope of the relationships between p.f.s./ΔP and $P_{1,s}$ markedly decreased with increasing atrial pressure. Because under condition *b* changes in $P_{1,s}$ could only be due to changes in atrial volume, it can be concluded that the 'sensitivity' of atrial receptors to alterations in the strength of atrial contraction that are due to volume changes, decreases as a consequence of increasing atrial volume.

Diastolic discharge

Responses to atrial volume changes as a function of peak diastolic atrial pressure

All the receptors but one (□) were activated by passive stretch of atrial muscle when atrial pressure and volume were increased (Fig. 1). Fig. 8 illustrates the relationships between peak diastolic firing rate and atrial pressure at the peak of the 'v' wave, during atrial volume changes performed under four different conditions, namely: condition *a* (ten units, Fig. 8*A*), condition *b* (eight units, Fig. 8*B*), condition *c* (eight units, Fig. 8*C*), and in the non-beating heart, condition *d* (five units, Fig. 8*D*).

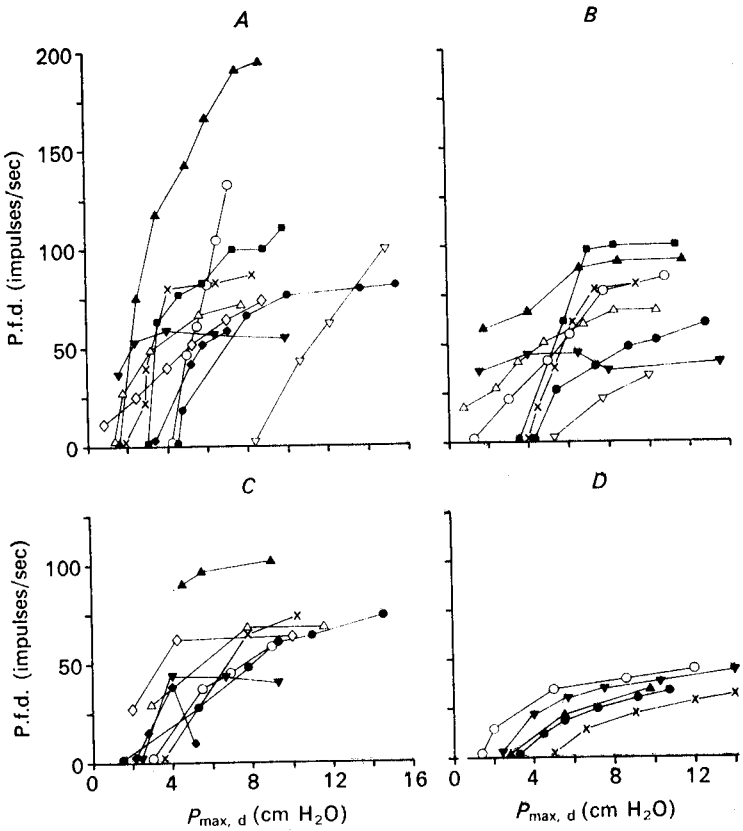

Fig. 8. Relationships between peak frequency of discharge in the diastolic train of impulses (p.f.d.) and peak diastolic atrial pressure ($P_{max.,d}$; peak of the 'v' wave) during changes in atrial volume. *A*, innervated hearts; ten receptors. *B*, denervated hearts; eight receptors. *C*, during vagal stimulation or ACh infusion; eight receptors. *D*, non-beating heart; five receptors. Explanation in the text.

For pressures ranging from 2 to 12 cm H_2O the diastolic discharge was higher with condition *a* than with *b* and *c*, and it was lowest with condition *d*. Fig. 3 (right, diastole) shows the average changes in peak diastolic firing rate for all the receptors studied. The difference between *a* and *b* was statistically significant ($P < 0{\cdot}05$; paired *t* test) at pressures ranging from 3 to 7 cm H_2O, and between *c* and *d* at pressures

ranging from 5 to 10 cm H_2O. Discharge rates under *b* and *c* were not statistically different.

In the non-beating heart atrial volume changes were produced by slow infusion of saline in order to assess the static response of the receptors (Recordati *et al.* 1975). As the atrium was distended, each receptor displayed a different threshold but a very similar sensitivity to increments in atrial pressure (Fig. 8*D*).

Systolic versus diastolic discharge

The difference between systolic and diastolic discharge in the same cardiac cycle (p.f.s. − p.f.d. = Δp.f.) has been calculated for six receptors. Fig. 9 shows the relationships between Δp.f. and $P_{1,s}$ for receptors studied under condition *a* (Fig. 9*A*) and *c* (Fig. 9*B*). It can be seen that Δp.f. was higher at low than at high atrial pressure and that, for the same pressure, it was higher for the receptors with higher spontaneous

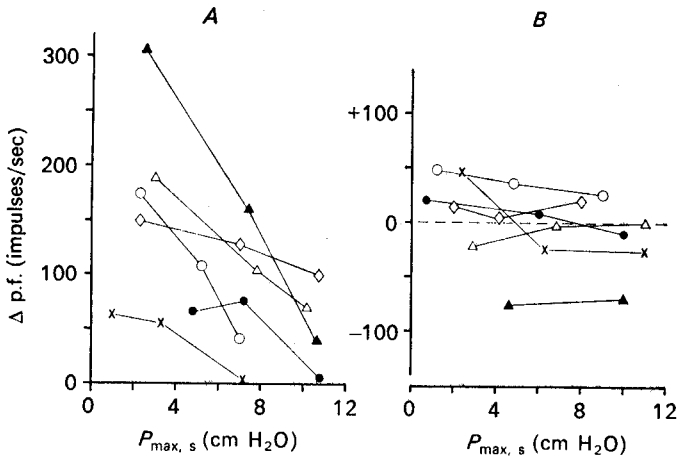

Fig. 9. Relationships between difference in the peak frequency of the systolic and diastolic trains of impulses in the same cardiac cycle versus peak systolic atrial pressure ($P_{max.,s}$). *A*, innervated hearts; six receptors. *B*, the same six receptors during vagal stimulation or ACh infusion. The zero line in *B* indicates the line of equality between systolic and diastolic firing rate. Below the zero line the peak firing rate during atrial filling was higher than during atrial systole.

firing rate. Under condition *c*, Δp.f. was lower than under condition *a* and four receptors displayed a higher frequency of discharge during atrial filling than during atrial systole (Δp.f. below the zero line in Fig. 9*B*). These findings indicate that the differences in the response of the receptors to active and passive stretch of atrial muscle might be diminished or even abolished by both increments in atrial volume and depression of atrial contractility.

DISCUSSION

Atrial receptors are mechanoreceptors sensitive to the stretch of that portion of atrial wall in which their endings are located (Paintal, 1973). Type A atrial receptors are normally sensitive to the stretch of atrial muscle produced by atrial contraction (active stretch), but as the atrial volume is increased they also become active during

the stretch of atrial wall produced by atrial filling (passive stretch). Because of the differences in the characteristics of the mechanical stimulus which excites receptor endings, the responses to active and passive stretch have been analysed separately.

Responses to active stretch

In a given inotropic state, changes in atrial volume alter the initial level of stretch and for any given atrial volume, changes in contractility modify the strength of atrial muscle contraction. Changes in volume may be defined as changes in the static component of stretch, and changes in contractility as alterations in the dynamic component of active stretch (rate of change in pressure and wall shortening) (Recordati *et al.* 1975, 1976).

In innervated hearts the response of each receptor to changes in atrial pressure was characteristic. Depression of contractility of atrial muscle caused by cardiac denervation and vagal stimulation, however, markedly lowered the frequency of discharge, increased the threshold to active stretch and modified the 'sensitivity' of the receptors to changes in atrial volume. These results indicate that the response to changes in the static component of the stimulus (initial level of active stretch) is strongly dependent on the dynamic component of the stretch. It is of significance that muscle receptors and cutaneous mechanoreceptors behave similarly, their responses to displacement being a function of the rate of displacement (Burgess & Perl, 1973). It has also been shown that when the rate of skin indentation is very high the usual response of cutaneous receptors to skin displacement (which is to increase their firing rate) can be converted into a decrease in the frequency of discharge (Burgess & Perl, 1973). Such a conversion might explain the fact that the two atrial receptors having the highest spontaneous firing rates under control conditions decreased their rate of discharge during increments in atrial volume. Hakumaki (1970), who reported a decrease in the firing rate of type A atrial receptors during atrial volume increases, might have been recording the activity only of receptors such as these, with a very high frequency of spontaneous discharge.

Under a given condition, the strength of contraction of atrial muscle may be altered by changes in atrial volume, as described by the Frank-Starling law of the heart (Payne, Stone & Engelken, 1971; Recordati *et al.* 1974). To investigate the effects of changes in the strength of contraction due to alterations in atrial volume, the responses of receptors have been analysed in denervated hearts, thus avoiding reflex alterations due to activation of baroreceptor reflexes. The systolic discharge did not increase for increments in peak systolic pressure above 4–5 cm H_2O, despite the fact that further increments in atrial volume resulted in further increases in the amplitude of the 'a' wave. Such a decreased 'sensitivity' to the strength of atrial muscle contraction might also be considered a decrease in the response to the dynamic component of the stimulus concomitant with increases in the static component. In this respect, type A receptors behave very much like the 'in series' muscle receptors, the Golgi tendon organs, which decrease their sensitivity to the strength of muscle contraction as the initial length of the muscle is increased (Stephens *et al.* 1975). This behaviour in Golgi tendon organs has been explained on the basis of muscle mechanics, considering that increases in preload are always accompanied by a simultaneous decrease in the rate of shortening (Stephens *et al.* 1975).

It may be concluded that at similar initial levels of stretch the systolic discharge of type A and Intermediate type receptors is dependent upon the contractility of atrial muscle, and that in a given contractile state the response to atrial systole is decreased by increasing the initial amount of stretch. These conclusions are also supported by the observations that increments in atrial contractility, like those produced by isoprenaline infusion after surgical cardiac denervation and electrical stimulation of the stellate ganglia (Recordati *et al.* 1976), always produced an increase in the systolic firing rate. Changes in receptor activity during both positive and negative inotropic interventions have been shown not to depend on changes in heart rate, since they were reproducible in paced hearts (Recordati *et al.* 1976).

Responses to passive stretch

All the receptors but one became active during atrial filling when their threshold to passive stretch was reached. The receptor that showed no response to passive stretch was the only one located above the junction of the azygos vein with the superior vena cava, thus confirming, as it has been recently demonstrated (Kappagoda, Linden & Mary, 1976, 1977), that the location of the receptors is an important determinant of the pattern of discharge. In a given contractile state and suprathreshold for passive stretch, the diastolic firing rate increased curvilinearly with increments in atrial pressure. However, as has been described for type B receptors (Recordati *et al.* 1975), the firing rate during atrial filling was lower with vagal stimulation than under control conditions, a decrease due to the decrease in the amplitude and rate of atrial filling.

Each receptor has a definitive location and orientation of its endings, and it is likely that its transducing properties are similar during systole and diastole. Hence, that the responses of a given receptor to atrial filling and contraction differ could be due to the different characteristics of the mechanical stretches affecting it during the cardiac cycle. In innervated beating heart, the receptors' responses to atrial systole had a characteristically higher frequency of discharge and lower threshold than the same receptors had during atrial filling. When atrial contractility was depressed, the responses to active and passive stretch were more similar, mainly due to a higher threshold to active stretch and a lower systolic firing rate. Depression of atrial contractility is known to affect markedly the dynamic component of active stretch (Recordati *et al.* 1976). Therefore in the innervated beating heart, the systolic and diastolic discharges of the same receptor differ mainly because during atrial contraction the dynamic component of the stretch acting on receptor endings is greater (Recordati *et al.* 1976).

Pattern of discharge

Kappagoda *et al.* (1976, 1977), demonstrated that the pattern of spontaneous discharge of an atrial receptor is mainly dependent upon its anatomical location. The present study confirms this observation. In innervated beating atrium each receptor showed a characteristic response to changes in atrial volume. In this condition it has been suggested that the stress–strain relationships could be different in different parts of the atrial wall (Kappagoda *et al.* 1976, 1977). Conversely in a distended, poorly contracting atrium, when the distribution of forces across the atrial wall is conceivably more uniform, different receptors had a very similar response to changes in

atrial volume. These conditions could also be described in terms of interactions between the static and dynamic components of stretch: when the dynamic component is very low, atrial receptors display a similar 'sensitivity' to the static component of stretch, which is in agreement with what Arndt *et al.* (1974) demonstrated in the non-beating atrium of the cat.

It should be noted, however, that atrial mechanoreceptors, like muscle and skin mechanoreceptors, display directional sensitivity, the response to a stretch depending also upon the direction of the stretch with respect to the orientation of the endings (Chapman & Pankhurst, 1976). An atrial receptor may have its endings functionally orientated so as to detect atrial filling ('in parallel' orientation), and it could be located in the atrial wall close to another receptor whose endings are functionally orientated so as to detect atrial contraction ('in series' orientation) (Whitteridge, 1953; Recordati *et al.* 1976). Such orientation of atrial endings would explain the following findings, which are in apparent contradiction to those reported by Kappagoda *et al.* (1976, 1977). First, in our present and previous studies, few type A atrial receptors have been located on the lateral free wall of the right atrium. Secondly, type A atrial receptors have been located by us and by other authors (Coleridge *et al.* 1957) at the junction of the superior vena cava with the right atrium, where type B receptors have also been located.

If the atrial endings have similar transducing properties (Arndt *et al.* 1974), then for a given location (Kappagoda *et al.* 1976, 1977) and orientation (Chapman & Pankhurst, 1976) of the endings, atrial dynamics, namely atrial volume and the state of atrial contraction, are the determinants of the pattern of discharge. Changes in atrial volume mainly affect the diastolic discharge while changes in the inotropic state mainly influence the systolic burst of impulses. These conclusions are strongly supported by the experiment shown in Fig. 4. A receptor which in control conditions had a type A pattern of discharge, after surgical cardiac denervation assumed an Intermediate pattern and was subsequently converted to a type B pattern during depression of contractility of atrial muscle. A decrease in the inotropic state, in fact, is always accompanied by a simultaneous increase in atrial dimensions (Recordati *et al.* 1974, 1975, 1976).

Almost all type A receptors could be converted into Intermediate type or type B receptors (Recordati *et al.* 1976; Kappagoda *et al.* 1976, 1977). Hence the comparative frequency of type B relative to type A or Intermediate type receptors might be highly dependent upon the state of atrial dynamics in a given experimental preparation, which would explain the disparities in the relative numbers of type A, type B and Intermediate type receptors reported by different investigators in cats, dogs, rabbits and monkeys (Kappagoda *et al.* 1976, 1977; Rao, Fahim & Gupta, 1975; Gupta, 1977).

This article was prepared, in part, during tenure of an Assistant Visiting Professorship at the Department of Physiology of the University of North Carolina, Chapel Hill, U.S.A. I am grateful to Ms Ellen Curtin for the editorial assistance.

REFERENCES

ARNDT, J. O., BRAMBRING, P., HINDORF, K. & RÖHNELT, M. (1971). The afferent impulse traffic from atrial A-type receptors in cats. Does the A-type receptor signal heart rate? *Pflügers Arch.* **326**, 300–315.

ARNDT, J. O., BRAMBRING, P., HINDORF, K. & RÖHNELT, M. (1974). The afferent discharge pattern of atrial mechanoreceptors in the cat during sinusoidal stretch of atrial strip *in situ*. *J. Physiol.* **240**, 33–52.

BURGESS, P. R. & PERL, E. R. (1973). Cutaneous mechanoreceptors and nociceptors. *Handbook of Sensory Physiology*, vol. 1, ed. IGGO, A., pp. 29–78. Berlin: Springer-Verlag.

CHAPMAN, K. M. & PANKHURST, J. H. (1976). Strain sensitivity and directionality in cat atrial mechanoreceptors *in vitro*. *J. Physiol.* **259**, 405–426.

COLERIDGE, J. C. G., HEMINGWAY, A., HOLMES, R. L. & LINDEN, R. J. (1957). The location of atrial receptors in the dog: a physiological and histological study. *J. Physiol.* **136**, 174–197.

GUPTA, B. N. (1977). The location and distribution of type A and type B atrial endings in cats. *Pflügers Arch.* **367**, 271–275.

HAKUMAKI, M. O. K. (1970). Function of left atrial receptors. *Acta physiol. scand.* suppl. **344**, 7–54.

KAPPAGODA, C. T., LINDEN, R. J. & MARY, D. A. S. G. (1976). Atrial receptors in the cat. *J. Physiol.* **262**, 431–446.

KAPPAGODA, C. T., LINDEN, R. J. & MARY, D. A. S. G. (1977). Atrial receptors in the dog and rabbit. *J. Physiol.* **272**, 799–815.

NEIL, E. & JOELS, N. (1961). The impulse activity in cardiac afferent vagal fibres. *Arch. Exp. Path. Pharmak.* **204**, 453–460.

PAINTAL, A. S. (1973). Vagal sensory receptors and their reflex effect. *Physiol. Rev.* **53**, 159–227.

PAYNE, R. M., STONE, H. L. & ENGELKEN, E. J. (1971). Atrial function during volume loading. *J. appl. Physiol.* **31**, 326–331.

RAO, P. S., FAHIM, M. & GUPTA, B. N. (1975). Relative distribution of types A and B atrial receptors in dogs, cats, monkeys and rabbits. *Experientia* **31**, 1174–1175.

RECORDATI, G. (1976). Responses of type A atrial vagal receptors to changes in atrial volume and contractility. *International Symposium on Cardiac Receptors.*

RECORDATI, G., LOMBARDI, F., BISHOP, V. S. & MALLIANI, A. (1975). Response of type B atrial vagal receptors to changes in wall tension during atrial filling. *Circulation Res.* **36**, 683–691.

RECORDATI, G., LOMBARDI, F., BISHOP, V. S. & MALLIANI, A. (1976). Mechanical stimuli exciting type A atrial vagal receptors in the cat. *Circulation Res.* **38**, 397–403.

RECORDATI, G., LOMBARDI, F., MALLIANI, A. & BROWN, A. M. (1974). Instantaneous dimensional changes of the right atrium of the cat. *J. appl. Physiol.* **36**, 686–692.

STEPHENS, J. A., REINKING, R. M. & STUART, D. G. (1975). Tendon organs of cat medial gastrocnemius: responses to active and passive forces as a function of muscle length. *J. Neurophysiol.* **38**, 1217–1231.

WHITTERIDGE, D. (1953). Electrophysiology of afferent cardiac and pulmonary fibres (abstr.). *Proc. int. Union physiol. Sci.* pp. 66–72.