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THE EFFECT OF STRETCHING THE SUPERIOR VENA CAVAL–RIGHT ATRIAL JUNCTION ON RIGHT ATRIAL RECEPTORS IN THE DOG

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SUMMARY

1. Action potentials were recorded from fibres in the right cervical vagus, the receptor endings of which were localized to the endocardial surface of the superior vena caval–right atrial junction.

2. Stretching the junction between the superior vena cava and the right atrium without obstructing venous return caused an increase in the discharge of these fibres. This increase in impulse frequency was similar to that caused by small changes in mean right atrial pressure (range 0–13·5 cm H_2O).

3. This evidence supports the earlier suggestion that stimulation of the right atrial receptors by stretching the superior vena caval–right atrial junction causes a reflex increase in heart rate.

INTRODUCTION

It has been shown that stretching the junction between the superior vena cava and the right atrium in the dog results in a reflex increase in heart rate (Kappagoda, Linden & Snow, 1970*a*, 1972). The afferent path of the reflex was shown to be in the vagal nerves and the efferent solely in the sympathetic nerves. These experiments did not provide any evidence as to the receptors involved in the reflex. However, atrial receptors have been demonstrated histologically in the endocardium of the intrapericardial portion of the superior vena cava (e.g. Nonidez, 1937; Miller & Kasahara, 1964), and it is suggested that these receptors were probably stimulated when the junction between the superior vena cava and the right atrium was stretched.

The present investigation was designed to locate the receptors that were stimulated when the junction between the superior vena cava and the right atrium was stretched using the technique previously described (Kappa-

goda *et al.* 1972). A preliminary report of this investigation has already been published (Kappagoda, Linden & Snow, 1970*b*).

METHODS

Dogs weighing between 18 and 27 kg were given a s.c. injection of morphine sulphate (0·5 mg/kg). One hour later under local anaesthesia (decicaine 2%) a catheter was introduced through a saphenous vein into the inferior vena cava and the dogs were anaesthetized with an intravenous infusion of a solution of α-chloralose (dose 0·12 g/kg; Establissments Kuhlmann, Paris). The anaesthetic solution consisted of 1 g chloralose, 0·72 g NaCl, 0·21 g $NaHCO_3$ dissolved in 100 ml. Dextraven 150 (Dextran 150 injection in 5% dextrose solution: Fisons Pharmaceuticals Ltd, Loughborough, England). Following the initial dose of anaesthetic 500,000 i.u. benzyl penicillin (Crystapen, Glaxo Laboratories Ltd, Greenford, England) were given I.V. To prevent occasional reflex muscular twitches disturbing the nerve preparation, the animals were paralysed by an injection of succinyl choline (dose 0·5 mg/kg, repeated every 15–20 min; Scoline: Allen & Hanbury Ltd, London). Since the depth of anaesthesia could not be assssed easily in a paralysed animal, doses of succinyl choline were periodically omitted, the animal permitted to recover from its effects, and the depth of anaesthesia assessed. A steady state of anaesthesia was maintained by further intravenous infusions of chloralose (approximately 10 mg/kg every 15 min).

As soon as possible after the induction of anaesthesia, the trachea was cannulated and artificial respiration was started with 40% O_2 using a modified Starling Ideal Pump (Ledsome, Linden & Norman, 1967). When the chest was opened, an expiratory resistance was provided by placing the expiratory outlet from the pump under 3 cm water.

The right side of the chest was opened through the fourth intercostal space and the azygos vein ligated 2 cm distal to its junction with the superior vena cava. A cannula (bore 5 mm: Redding left atrial cannula, Portland Plastics Ltd, Hythe, Kent) modified by the incorporation of two distensible latex balloons was inserted through the external jugular vein into the superior vena cava. The details of the relevant parts of the cannula and the anatomy are illustrated in Fig. 1. The balloon *A* was placed at the junction between the superior vena cava and the right atrium, distension of this balloon stretched the atrio-caval junction. The balloon *B* was placed in position caudal to the right costocervical–vertebral venous trunk and during distension the superior vena cava was occluded completely. The blood accumulating in the superior vena cava was pumped away by a variable speed roller pump, and returned to the animal through the right femoral vein; the pressure in the superior vena cava above the occluding balloon was controlled and maintained constant. Coagulation of the circulating blood was prevented by an I.V. injection of heparin B.P. (dose 500 i.u./kg followed by 50 i.u./kg every hour; Pularin, Evans Medical Ltd). The pump was primed with 250 ml. Dextraven 150 (Fisons Pharmaceuticals Ltd). The junction between the superior vena cava and the right atrium could then be stretched by distending the balloon *A* with warm saline (NaCl 0·9 g/100 ml. at 38° C) without changing the venous return to the heart or the pressures in the superior vena cava and the right atrium. Pressures in the cardiovascular system were recorded through short (about 10 cm long) nylon catheters (Portex Surgical quality No. 4, Portland Plastics Ltd) inserted into the right femoral artery and the right atrium through the atrial appendage. The pressure in the superior vena cava was measured through a cannula incorporated in the wall of the main cannula inserted into the superior vena cava as shown in Fig. 1. Pressure in the trachea was also

recorded. All the cannulae were attached to strain gauge manometers (Model P23Gb; Statham Instruments Inc., Hato Rey, Puerto Rico), and after amplification by means of carrier and driver amplifiers (EMMA 4000 system, S.E. Laboratories Ltd, Feltham, Middlesex), the pressures were recorded by a direct writing U.V. recorder (Model 2100: S.E. Laboratories Ltd).

The systems used for recording the femoral and right atrial pressures were flat (±5%) to 60 c/sec as tested by the method of Adrill, Fentem & Wellard (1967). Mean pressure in the right atrium was obtained by passing the carrier amplifier output through a RC network with a 2 sec time constant incorporated in the driver

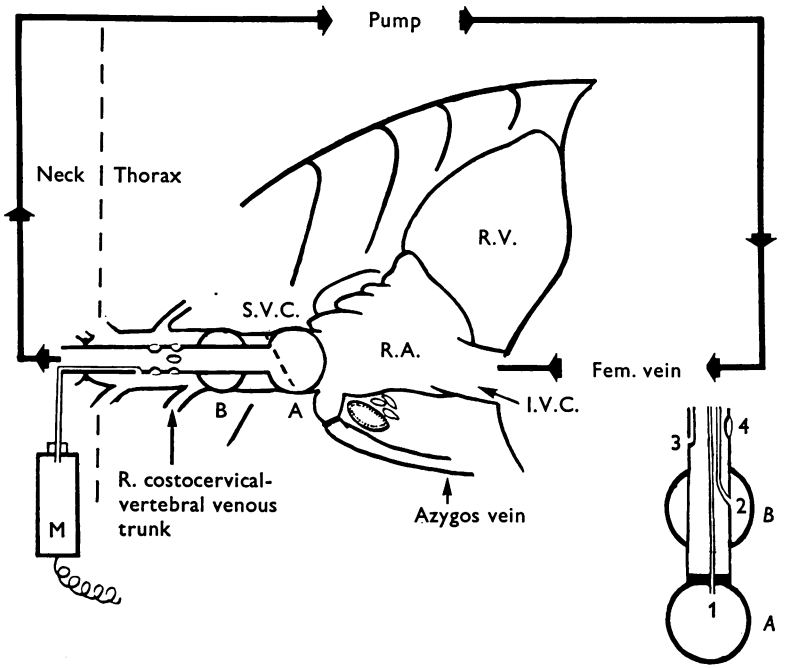

Fig. 1. Diagram of experimental preparation: S.V.C. and I.V.C., superior and inferior venae cavae; R.A. and R.V., right atrium and ventricle; M, strain-gauge manometer. A cannula incorporating two balloons (*A* and *B*) is inserted into the superior vena cava through the external jugular vein. Inset is a diagram of the end of the cannula to show orifices to balloon *A* (1), to balloon *B* (2), for recording of pressure in superior vena cava above the point of occlusion (3) and one of several orifices in the cannula through which the blood is aspirated (4). The balloon *B* acts as a cuff which occludes the superior vena cava. The blood accumulating in the superior vena cava is pumped away through the cannula and returned to the animal via the femoral vein. The junction between the superior vena cava and the right atrium may then be stretched by distending the terminal balloon *A* without interfering with venous return to the heart. The balloon *B* must be located caudal to the entrance of the right costocervical-vertebral venous trunk in order to ensure that the venous return is not obstructed when the balloon *A* is distended. The interrupted line across the superior vena cava indicates the reflexion of the visceral pericardium at the parietal surface visible in the preparation as a pale line.

amplifier. The pressure in the superior vena cava was recorded as a steady mean pressure and no added damping was required. The mean pressure in the femoral artery was calculated by adding 1/3 the pulse pressure to the diastolic pressure. The strain gauge manometers were calibrated in a stepwise manner using saline and mercury manometers. Zero pressures were recorded post mortem for each manometer as the pressure recorded with the tip of the cannula free in air. The signal from the femoral pressure was used to drive a cardiotachometer (Gilford Instrument Laboratories Inc., Oberlin, Ohio, U.S.A.) and the analogue output of this was recorded on the U.V. recorder. The e.c.g. was recorded from electrodes applied to the right foreleg and the left hind leg. The end-tidal P_{CO_2} was monitored continuously and recorded by aspirating air from the trachea into an I.R. carbon dioxide analyser (URAS, Hartman & Braun, Frankfurt Main, West Germany).

Samples of arterial blood were withdrawn anaerobically at intervals throughout the experiment and the pH, P_{CO_2} and P_{O_2} were measured as described by Ledsome, Linden, Norman & Snow (1967). The P_{CO_2} and pH were maintained within normal limits by adjusting the ventilation or by I.V. infusions of $NaHCO_3$ (8·4 g/100 ml.). The rectal temperature was measured using a telethermometer probe (Yellow Springs Instrument Co. Ltd, Ohio, U.S.A.) and maintained at 37·5 ($\pm$ 1)° C by adjusting heating lamps above and below the animal.

Technique for recording action potentials

Action potentials in slips of the vagus were recorded in the usual way (Coleridge, Coleridge & Kidd, 1964). Briefly the right vagus was dissected away from the common carotid artery in the neck and the sheath removed. The nerve was placed on a black Perspex platform and further dissection and preparation of slips of nerve carried out under liquid paraffin. Each fine slip was placed on a pair of bipolar silver electrodes connected to a pre-amplifier (Model 122, Tectronix Inc., Cleveland, Ohio); the output from this pre-amplifier after further amplification by a driver amplifier (EMMA 4000 System, S.E. Laboratories Ltd) was recorded on the U.V. recorder (Model 2100, S.E. Laboratories Ltd). The output from the pre-amplifier was displayed on the screen of an oscilloscope and also connected through an audio-amplifier to a loudspeaker. The balloon *A* was then distended and, if a change in impulse frequency was noted, the slip was further dissected until a recording of a single unit, which responded to balloon distension with a change in the trains of impulses, was obtained.

The mean pressure in the right atrium was changed in three dogs by bleeding and by I.V. infusion of Dextraven 150 and the effect of such changes on the impulse frequency in the single unit was studied.

Location of receptors

After the effect of balloon distension on the impulse frequency of each single unit had been studied the precise location of the receptor ending was determined by the following procedure. The epicardial surface of the right atrium was gently probed with a glass rod. When the rod made contact with the approximate area of localization, there was a sharp burst of activity in the single unit. The animal was then killed by opening the aorta and allowing the blood to flow into the abdomen. The right atrium was opened and the blood sucked away. The endocardial surface was then probed with a fine glass rod and when the probe made contact with the receptor ending there was a sudden sharp rise in the impulse frequency of the single unit. Finally, when the process of punctate localization has been completed under direct vision, the precise area of tissue deep to the point of stimulation was crushed with fine forceps in steps of approximately 0·5 mm up to a depth at which stimulation of the small area with the fine glass rod no longer resulted in any response.

RESULTS

Experiments were performed on a total of fifteen dogs. Nine single units responding to distension of the balloon were obtained in nine animals. In the other six animals a variety of single units having cardiac and respiratory rhythms were obtained but these units showed no response to balloon distension and were not studied further.

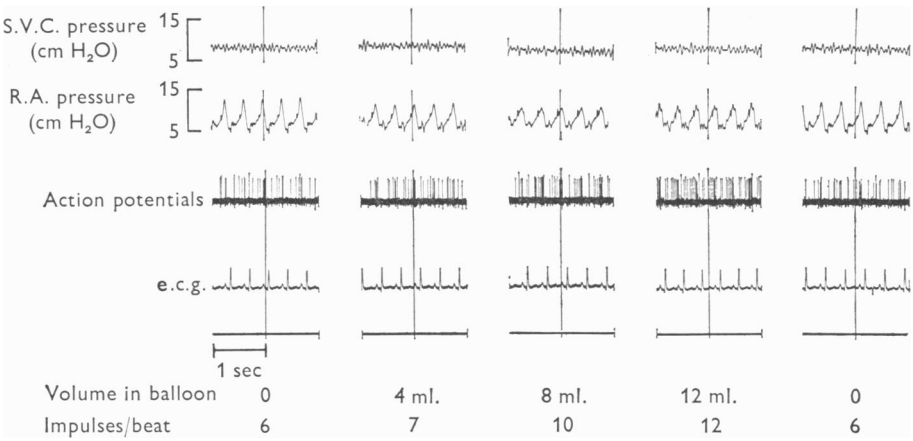

Fig. 2. Effect of stretching the junction between the superior vena cava and the right atrium on a single unit in the cervical vagus. Each panel of experimental record shows from above downwards the superior vena caval (S.V.C.) pressure, right atrial (R.A.) pressure, action potentials from a slip of the right cervical vagus and electrocardiogram (e.c.g.). As the volume in the terminal balloon *A* was increased in increments of 4 ml. (i.e. as the superior vena caval–right atrial junction was stretched) the impulse frequency (impulses/beat) increased from 6/beat to 12/beat. The impulse frequency returned to the control value after the release of the distension. This particular single unit showed a discharge during atrial filling and during atrial systole.

Recording commenced approximately 2–3 hr after the initial anaesthetic. At the beginning of recording the blood pressure was 137·5 mm Hg (mean; range 109–159) and the heart rate was 144·8 beats/min (mean; range 60–185). The pH, P_{CO_2} and P_{O_2} were 7·38 (mean; range 7·37–7·41), 39·1 mm Hg (mean; range 31–44·5 mm Hg) and 208 mm Hg (mean; range 195–243 mm Hg) respectively.

When a single unit responding to balloon distension was obtained the following experimental protocol was followed. Control records were taken for a period of 1 min. This was followed by distension of the terminal balloon with warm saline in increments of 2 ml. up to a total of 10–12 ml. In three dogs, this warm saline was injected in increments of 4 ml. Each

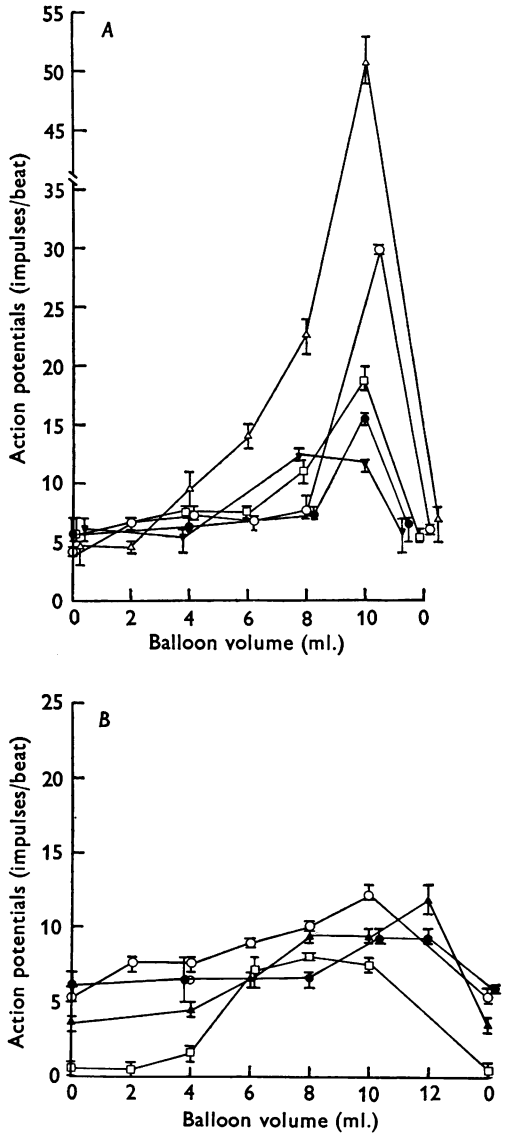

Fig. 3. Effect of stretching the junction between the superior vena cava and the right atrium on the nine single units in the right cervical vagus. The impulse activity (impulses/beat) is shown plotted against the distending volume (ml.). Each symbol represents a single unit and the bars represent ranges. *A* illustrates the behaviour of the single units which showed a sharp increase in impulse frequency, and *B* illustrates the behaviour of the single units which showed a gradual increase in impulse frequency when the terminal balloon was distended.

distension was maintained for 20 sec and records were obtained. Finally the distension was removed and a second control record obtained. This procedure was repeated at least twice for each single unit. The impulse activity in the single unit was calculated as the mean of ten consecutive heart beats and is expressed as impulses/beat. Records from a typical experiment are shown in Fig. 2. The impulse frequency in the control period was 6 impulses/beat and it increased to 7, 10 and 12 impulses/beat when 4, 8 and 12 ml. saline were injected into balloon *A* respectively. The impulse frequency returned to 6 impulses/beat during the second control period. There was no change in heart rate.

The responses of the nine single units to balloon distension fell into two groups. Five of the units studied showed a moderate increase in impulse frequency up to a distending volume of 6–8 ml. and further distension caused a sharp increase in impulse frequency. These results are illustrated in Fig. 3*A*. The other four single units showed a moderate gradual increase in impulse frequency with increasing distending volumes. These results are illustrated in Fig. 3*B*.

Adaptation

In order to determine whether the single units showed evidence of adaptation, in six single units, the maximum distension was maintained for a period of 1 min. There was a moderate degree of adaptation in two of the single units studied but the other four units maintained their impulse frequency throughout the period of distension. An example of each type of response is illustrated in Fig. 4.

Effects of changes in mean right atrial pressure

In three dogs after the effect of graded distensions of balloon *A* had been studied, the mean right atrial pressure was altered either by bleeding or by transfusions of Dextraven. It was therefore possible to compare the effect on the impulse activity of the same unit, of changes in mean right atrial pressure and of graded stretching of the superior vena caval–right atrial junction by balloon distension. The effects of these two methods of stimulation on the impulse activity in the three units is illustrated in Fig. 5. For example, in the unit illustrated in Fig. 5*A*, the impulse activity increased from a control value of 6 impulses/beat (range 5–7) to 9·3 impulses/beat (range 9–10) when the superior vena caval-right atrial junction was stretched by injecting 10 ml. of saline into the terminal balloon *A*. The same unit had its impulse activity increased from 2·5 impulses/beat (range 2–3) to 7 impulses/beat when the mean right atrial pressure was increased from a control value of 0 cm H_2O to 10 cm H_2O. The behaviour of the remaining two units (Fig. 5*B* and *C*) was also quali-

tatively similar to that of the unit illustrated in Fig. 5*A*. Thus stimulating all three units by balloon distension produced an increase in impulse activity similar to that caused by small changes in mean right atrial pressure; the highest pressures recorded in the case of the three units illustrated in Fig. 5*A*, *B* and *C* being 10, 13·5 and 10 cm H_2O respectively.

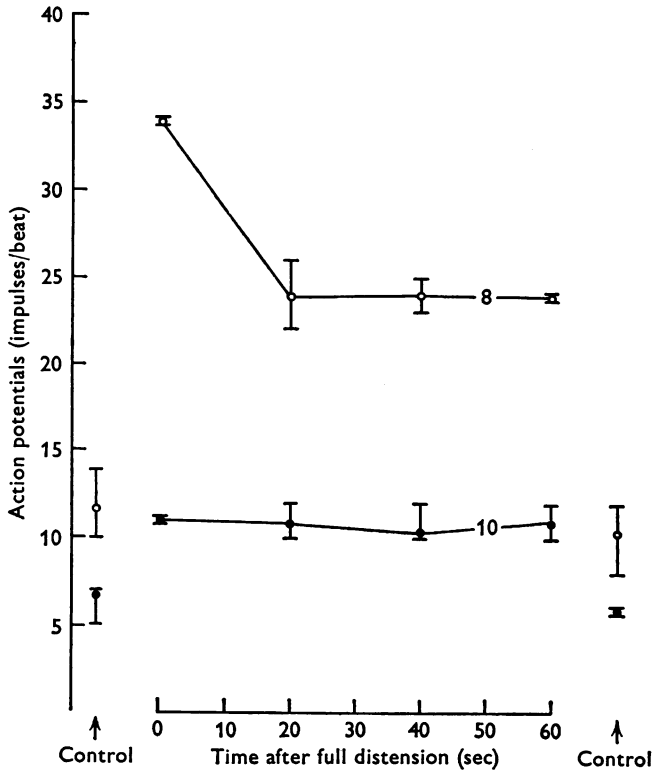

Fig. 4. Effect of prolonged stretching of the junction between the superior vena cava and the right atrium on single units in the right cervical vagus. The impulse activity (impulses/beat) is plotted against time (sec) after completion of the distension. The unit (●) was stimulated with a distension of 10 ml. saline into balloon *A* (Fig. 1). The unit (○) was stimulated with a distension of 8 ml. of saline. The bars represent ranges.

Localization

The stages in the localization of the receptor endings are illustrated in Fig. 6. All nine single units were judged to be in the endocardium of the intrapericardial portion of the superior vena cava because destruction up to a depth of about 1·5 mm from the surface with fine forceps abolished the response. It was apparent that five single units which responded with a sharp increase in impulse frequency were located on the endocardium

immediately adjacent to the balloon *A* (Fig. 3*A*). The remaining four units which responded with a gradual increase in impulse frequency were located further away (approximately 1·5 cm) from the ring of tissue immediately surrounding balloon *A* (Fig. 3*B*). The location of each receptor is indicated in the diagrams in Fig. 7.

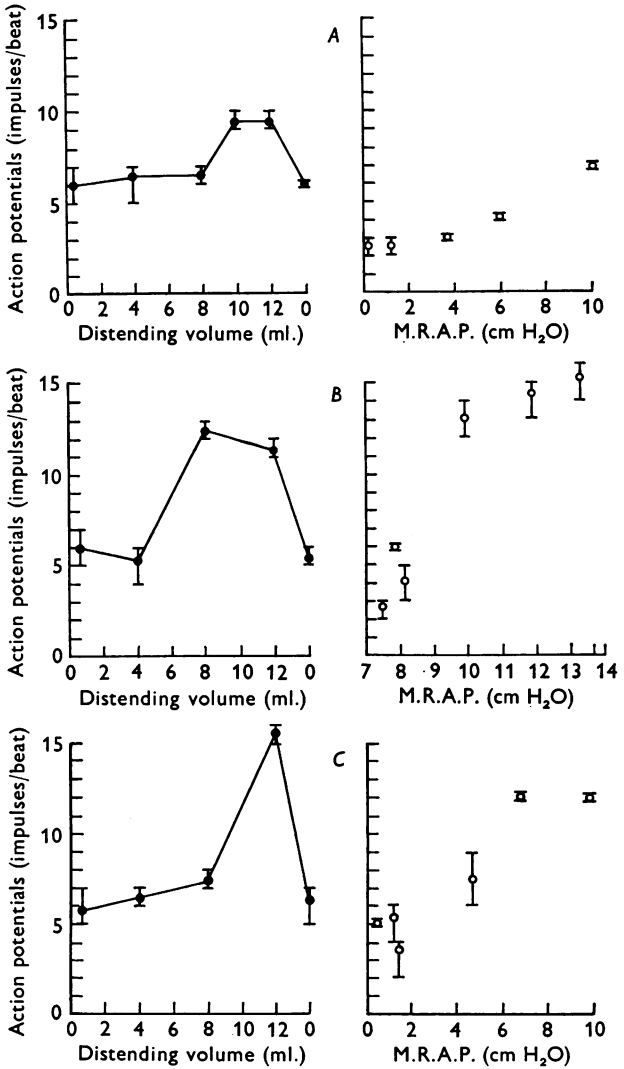

Fig. 5. Comparison of the effect of stretching the superior vena caval-right atrial junction (symbol ●) and changing the mean right atrial pressure (M.R.A.P., symbol ○) on three single units (*A*, *B*, and *C*) in the right cervical vagus. Impulse activity (impulses/beat) is plotted against distending volume (ml.) and against mean right atrial pressure (cm H_2O). The bars represent ranges of responses.

DISCUSSION

It has previously been shown that distension of the junction between the superior vena cava and the right atrium results in a reflex increase in heart rate; the efferent pathway is solely in the sympathetic nerves to the heart and the afferent pathway at least partially in the vagus (Kappagoda

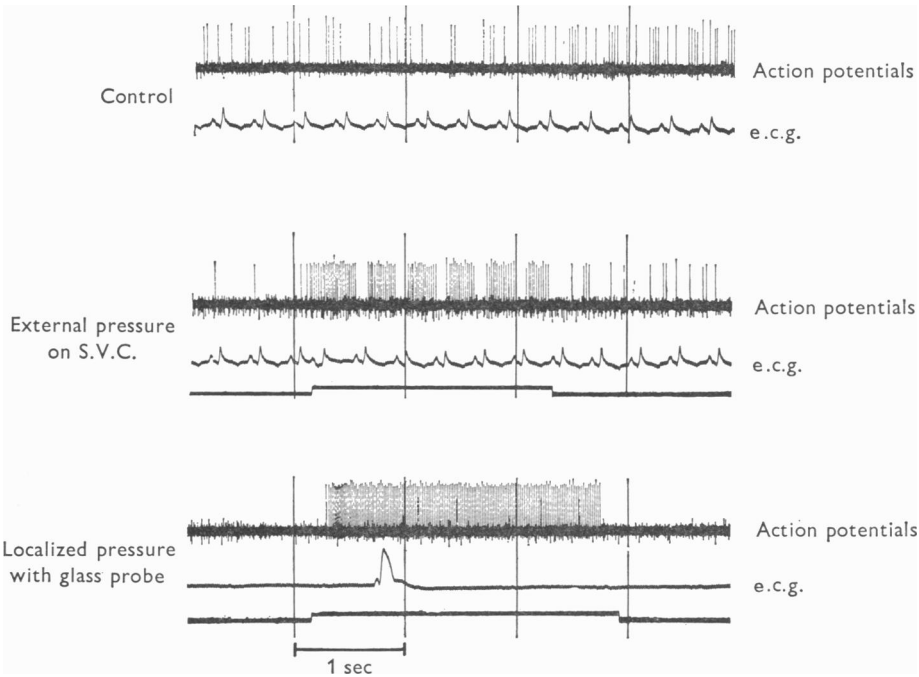

Fig. 6. The stages in the localization of a receptor on the endocardial surface of superior vena caval right atrial junction. The effect of balloon distension on this receptor is shown in Fig. 2. Each panel shows records of the action potentials from the cervical vagus and the electrocardiogram. After approximately localizing the receptor by external pressure, the animal was killed and the right atrium opened. The final record was obtained by gentle pressure on a small area of endocardium (approximately 1 mm^2) in the vicinity of the balloon *A* (Fig. 1).

et al. 1972). Also atrial receptors (unencapsulated nerve endings) have been demonstrated at the junction of the superior vena cava and right atrium (e.g. Nonidez, 1937; Miller & Kasahara, 1964) and these receptors have been shown to give rise to trains of impulses in fibres in the vagus (Coleridge, Hemingway, Holmes & Linden, 1957).

The results of the present investigation show that stretching the junction between the superior vena cava and the right atrium using balloons

stimulates only the atrial receptors previously described and results in an increase in the frequency of impulses in fibres of the right vagus.

Localization of receptor endings

All the single units which were stimulated by balloon distension were localized, in the manner described, to the endocardial portion of the superior vena cava. Using this technique all atrial receptors should respond with a high frequency continuous discharge to a light pin point stimulus over a small area of less than 1 mm^2 and should cease to function after destruction of the endocardium within 1·5 mm of the surface. Unless this type of test, or histology of the located area instead of destruction of the

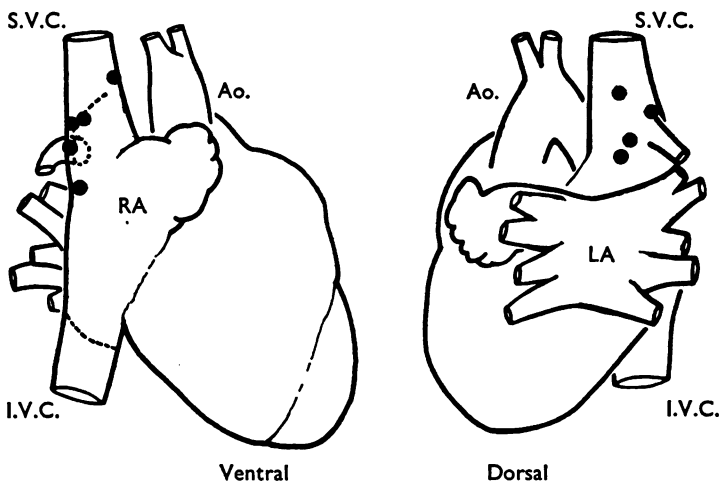

Fig. 7. The location of the receptor endings which were stimulated by stretching the junction between the superior vena cava (S.V.C.) and the right atrium (R.A.). L.A. left atrium; Ao. Aorta; I.V.C. inferior vena cava. Each spot denotes one receptor ending from one dog.

endocardium (e.g. Coleridge *et al.* 1957), is completed it is not possible to conclude that the trains of impulses observed in vagal nerve fibres originate in atrial receptors. Also precise localization of the receptor endings is necessary so as to exclude the possibility that receptors other than those located in the heart are being stimulated by balloon *A*. Previous workers (e.g. Paintal, 1953; Henry & Pearce, 1956) relied on techniques for localization which consisted of obstructing the outflow from the chambers of the heart. Though these methods may localize receptors to those regions of the heart proximal to the obstruction, they do not allow the conclusion that the receptors are located on the endocardial surface of any particular chamber.

Effect of balloon distension

In these experiments no attempt was made to demonstrate the increase in heart rate which occurs when the junction between the superior vena cava and the right atrium is stretched because a variable portion of the cervical vagus was destroyed before a single unit responding to balloon distension was obtained.

All nine single units showed an increase in impulse frequency to balloon distension but the characteristics of the response varied. It was found that five of the single units responded with a sudden sharp increase in impulse frequency at the higher distending volumes (8 ml.) whereas the remaining four showed a gradual increase in impulse frequency. This difference in the pattern of response was related to the position of the receptor in relation to the distending balloon. Those receptors located close to the balloon had a sharp increase in impulse frequency at the larger volumes and it is possible that this was caused by direct contact of the balloon with the endocardium where the receptor was located. The receptors located further away from the balloon showed a gradual increase in impulse frequency which, presumably resulted from that part of the atrial wall being stretched as the balloon was distended. Thus it seems likely that the difference in the patterns of response observed in this investigation is an artifact of the experimental method of stimulation and is not evidence for the existence of two different groups of receptors.

Effects of changes in right atrial pressure

Stimulation of the receptors at the junction between superior vena cava and the right atrium by balloon distension cannot be described as physiological. The same receptors were therefore subjected to a more physiological type of stimulation; changes in right atrial pressure. The results obtained clearly demonstrated that these receptors responded to small changes in the mean right atrial pressure in a manner that was comparable to the response evoked by balloon distension in that the trains of impulses evoked by balloon distension and by changes of atrial pressure of up to 13·5 cm H_2O were the same. These changes in atrial pressure are well within the physiological range.

It is therefore concluded that the evidence presented supports the earlier suggestion that stretching the junction between the superior vena cava and the right atrium by balloon distension stimulates the right atrial receptors and changes in activity in these receptors are responsible for the observed reflex increase in heart rate reported previously (Kappagoda *et al.* 1972).

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