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NERVOUS ACTIVITY OF AFFERENT CARDIAC SYMPATHETIC FIBRES WITH ATRIAL AND VENTRICULAR ENDINGS

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SUMMARY

1. We recorded the electrical activity of single afferent cardiac fibres isolated from the third and fourth left thoracic sympathetic rami communicantes of anaesthetized cats. Their conduction velocities ranged from 12 to 32 m/sec.

2. The endings of each fibre were localized to one cardiac chamber by mechanical probing of the opened heart performed at the end of the experiment.

3. The impulse activity was spontaneous and, in fibres with atrial or ventricular endings, it was in phase with a particular atrial or ventricular event.

4. This nervous activity increased during increases in pressure occurring in the chamber where the endings were located. Conversely, decreases in pressure were accompanied by decreased nervous discharge.

5. In some experiments the left coronary artery was perfused at different flows and pressures. Brief decreases or increases in coronary flow and pressure decreased or increased, respectively, the discharge of fibres with atrial or ventricular endings. Fibres were excited by intracoronary injections of veratridine.

6. Cessation of coronary pump flow increased the discharge of fibres with atrial or ventricular endings only when myocardial ischaemia was accompanied by signs of heart failure.

7. These afferent cardiac sympathetic fibres which provide the spinal cord with continuous specific information on cardiac events are likely to contribute to the neural control of circulation.

INTRODUCTION

Edgeworth (1892) first suggested the existence in the cardiac sympathetic nerves of afferent fibres which he called 'sympathetic sensory fibres'. Following that report, other workers obtained more complete evidence of sympathetic sensory endings in the heart (Woollard, 1926; Nettleship, 1936; Nonidez, 1939; Hirsch & Orme, 1947; Khabarova, 1963; Hirsch, Nigh, Kaye & Cooper, 1964). This afferent pathway has been demonstrated to be involved in transmitting the impulses signalling cardiac pain, both in man (Lindgren & Olivecrona, 1947; White, 1957) and in experimental animals (Sutton & Lueth, 1930; Brown, 1967). In addition, it is involved in spinal sympathetic reflexes elicited by cardiovascular stimuli (Malliani, Schwartz & Zanchetti, 1969; Brown & Malliani, 1971; Malliani, Pagani, Recordati & Schwartz, 1971; Malliani, Peterson, Bishop & Brown, 1972).

The possibility that afferent cardiac fibres running in the sympathetic nerves, henceforth referred to as *afferent cardiac sympathetic fibres*, might also send continuous information to the spinal cord on normal cardiac events has been completely overlooked. This function has been attributed exclusively to afferent cardiac *vagal* fibres.

We, therefore, studied afferent cardiac sympathetic fibres whose impulse activity was in phase with the heart beat and whose endings were in the atria and ventricles. Preliminary accounts of this work have been published (Malliani, Recordati, Schwartz & Pagani, 1971, 1972).

METHODS

The results were obtained from forty-eight experiments on cats (2·5–4·0 kg), anaesthetized by I.P. injection of pentobarbitone (35 mg/kg). The trachea was cannulated. Polyethylene catheters were inserted into (1) a carotid or a femoral artery, (2) the right atrium through the external jugular vein, (3) a femoral vein and (4) the left atrium through the atrial appendage (nine experiments). All cats were artificially ventilated after the I.V. injection of gallamine triethiodide 2 mg/kg (Sincurarina, Farmitalia). The pump was set as to provide an arterial P_{O_2} of 85–105 mm Hg, P_{CO_2} of 30–44 mm Hg and pH of 7·33–7·42. Three cats were breathing spontaneously during the first part of nervous recordings. Both vagi were cut in the neck.

In all animals artificially ventilated, the thorax was opened through the fourth left interspace. The fifth and sixth ribs on the left side were removed. The pericardium was cut in thirty-nine experiments; in nine animals it was left intact until nervous activity was recorded.

In six experiments the left coronary artery was perfused (Brown, 1968). These animals were heparinized (1000 u. I.V. initially and 500 u./hr later).

Threads were passed loosely around the thoracic aorta, the pulmonary artery and the inferior vena cava. Transient constrictions of these vessels were produced by pulling the ends of the threads through polyethylene tubes.

The heads of the second and third ribs were removed retropleurally on the left side to expose the stellate ganglion and its branches. The ganglion was covered by a pool of mineral oil maintained at body temperature by thermal radiation.

Variables recorded. We measured the pressure in the carotid or femoral artery, in both atria and in the inflow coronary arterial line with Statham P23Dc and P23De strain gauges. The flat ($\pm 5\%$) frequency responses of these systems were 15–30 Hz as calculated by the response to a step input of pressure (Fry, 1960). We also recorded the e.c.g. using a Grass 7P511 preamplifier, the heart rate using a Grass 7P4C tachograph and respiratory movements transduced by a crystal capsule connected to the side arm of the tracheal cannula. All of the variables were registered on a multichannel inkwriter polygraph (Grass P7).

Afferent nervous activity was recorded from filaments isolated under a dissecting microscope from the cut peripheral end of the third and fourth (T3, T4) left thoracic sympathetic rami communicantes. Filaments were split until discharges from a single active fibre were present. The filaments were laid across platinum electrodes which were connected to a.c. preamplifiers (Grass Model P511) with a band width of 10 Hz–10 kHz. Nervous activity and all variables recorded on the polygraph were fed into a tape recorder (Hewlett-Packard 3907C). Five of these variables could also be photographed by a Grass C4 camera from a slave cathode-ray tube arranged in parallel with a Tektronix 565 oscilloscope.

Measurement of conduction velocities of afferent fibres. Conduction velocity was determined for five fibres in five experiments. The left inferior cardiac nerve was isolated from the surrounding tissues above the aortic arch. This portion of the nerve was stimulated via platinum electrodes (interelectrode distance of 50 mm; cathode proximal). Stimuli were led from an isolation unit (Grass SIU) connected to a square-wave stimulator (Grass S4). Pulses were monophasic, 0·1 msec in duration, 3–5 V. The temperature of perinerve tissues was measured with a thermistor and maintained at about 37° C by thermal radiation.

Conduction velocity was calculated from the distance between the proximal stimulating electrode and the closest recording electrode divided by the time from the stimulus artifact to the beginning of the action potential.

Drugs injected. Veratridine (Aldrich Co.), 1–10 μg in 0·1–0·2 ml. saline, was injected into the coronary perfusion circuit as in previous experiments (Brown & Malliani, 1971). Noradrenaline (Noradrec, Recordati) 1–10 μg and angiotensin (Hypertensin, Ciba) 0·5–5 μg were injected I.V. as pressor drugs.

Localization of the afferent endings. The endings of each fibre in this report were localized to one cardiac chamber by mechanical probing performed after the animal had been killed and the heart opened. The probing was performed on both internal and external surfaces of cardiac walls, with sharp and blunt needles. Therefore, not more than one fibre could be obtained from each successful experiment.

Results as described were collected from animals having systolic blood pressures above 90 mm Hg and with rectal temperatures between 37 and 38·5° C.

RESULTS

We studied forty-eight afferent sympathetic fibres whose spontaneous nervous activity was in phase with cardiac rhythm and whose endings were excited by direct mechanical probing of the opened, non-beating heart. Twenty-seven endings were localized to the left atrium, ten to the right atrium, seven to the left ventricle and four to the right ventricle.

Spontaneous nervous activity of afferent cardiac sympathetic fibres with atrial endings. An example of this spontaneous impulse activity is shown in Fig. 1*a*. The general characteristics of the discharge of all atrial receptors were that (1) it consisted of, at most, one action potential per cardiac cycle and each cardiac cycle was not necessarily accompanied by a nervous

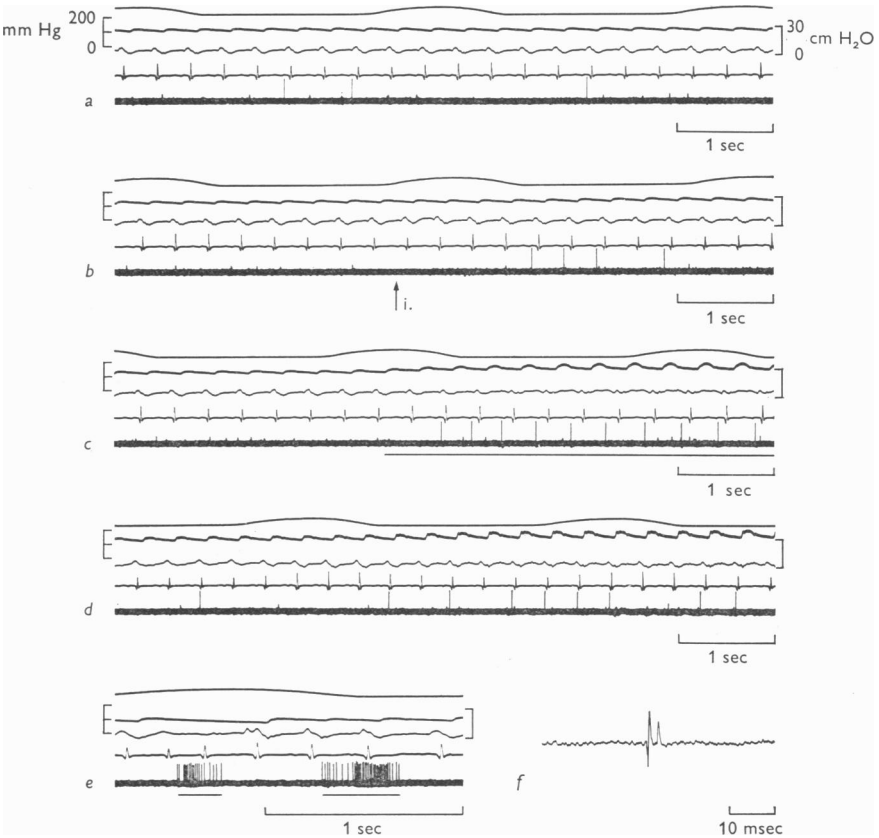

Fig. 1. Activity of a fibre with left atrial endings. Tracings in *a*, *b*, *c*, *d*, *e*, represent, from top to bottom, the endotracheal pressure (inflations upwards), the arterial blood pressure, the right atrial pressure, the e.c.g. and the nervous recording. *a*, Control. *b*, Injection, starting at the arrow, of 2 ml. warm saline. *c*, Constriction of the thoracic aorta. *d*, Beginning of a rise in arterial blood pressure produced by the I.V. injection of 3 μg noradrenaline. *e*, Mechanical probing of an area of the left atrium performed on the beating heart. *f*, Electrical stimulation of the left inferior cardiac nerve activating the afferent fibre; the biphasic first deflexion is the artifact of the stimulus, while the second upward and smaller deflexion is the action potential of the fibre. The approximate length of the fibre was 7 cm (see Methods). The conduction velocity calculated for this fibre was 32 m/sec.

impulse; and (2) there was a temporal relation between the action potential and a particular intra-atrial pressure wave.

We found fibres discharging in phase with atrial systole (*a* wave of the atrial pressure, Fig. 1*a*), with bulging of the atrio-ventricular valves (*c* wave), with atrial filling (*v* wave). For some fibres a particular phasic pattern of spontaneous discharge was constant for periods of about one to two hours. However, a particular pattern could also change spontaneously into another pattern.

A possible limitation of these observations was that recordings were obtained from artificially ventilated cats with chest and pericardium opened. Therefore, we attempted to verify whether afferent fibres with atrial endings had a similar impulse activity when the animal was breathing spontaneously. In two experiments, we identified two fibres whose discharge had the general characteristics described above. Opening of the thorax and of the pericardium did not grossly modify the firing of these fibres whose endings were subsequently found to be in the left atrium.

The discharge of five other fibres (three with left and two with right atrial endings) was also unchanged by the incision of the pericardium.

Effects of various haemodynamic stimuli. The discharge of afferent cardiac sympathetic fibres with atrial endings was increased during rises in atrial pressure. Examples are shown in Fig. 1, illustrating the effects of the intravenous injection of 2 ml. warm saline (Fig. 1*b*), of the constriction of the thoracic aorta (Fig. 1*c*) and of the I.V. injection of noradrenaline (Fig. 1*d*). A preliminary mechanical probing of an area of the left atrium, performed while the heart was beating, is shown in Fig. 1*e*. The electrical stimulation of the left inferior cardiac nerve (Fig. 1*f*) was used in order to calculate the conduction velocity, as described under Methods.

Four fibres with left atrial endings had conduction velocities between 12 and 32 m/sec (average 20·6 m/sec). Therefore, the fibres were medullated, belonging probably to the group Aδ (Gasser & Grundfest, 1939; Burgess & Perl, 1972).

The discharge of eleven atrial fibres (eight with left and three with right atrial endings) was studied during acute bleeding of the animal (30–60 ml. in 3–6 min). The discharge of each fibre was clearly reduced or even abolished. This is similar to what has been reported for atrial afferent vagal fibres (Gupta, Henry, Sinclair & von Baumgarten, 1966; Recordati, Schwartz, Pagani, Malliani & Brown, 1971).

Spontaneous nervous activity of afferent cardiac sympathetic fibres with ventricular endings. An example of this spontaneous impulse activity is shown in Fig. 3*a*. The general characteristics of the discharge of all ventricular receptors were that (1) it consisted of, at most, one action potential per cardiac cycle (following the onset of the Q waves of the e.c.g. by

40–120 msec); (2) not all of the cardiac cycles were accompanied by a nervous impulse.

A similar impulse activity was recorded from a fibre with left ventricular endings while the animal was breathing spontaneously. Opening of the thorax and the pericardium did not alter the general characteristics of the discharge. Another fibre from the left ventricle was found to have the same impulse activity before and after incision of the pericardium.

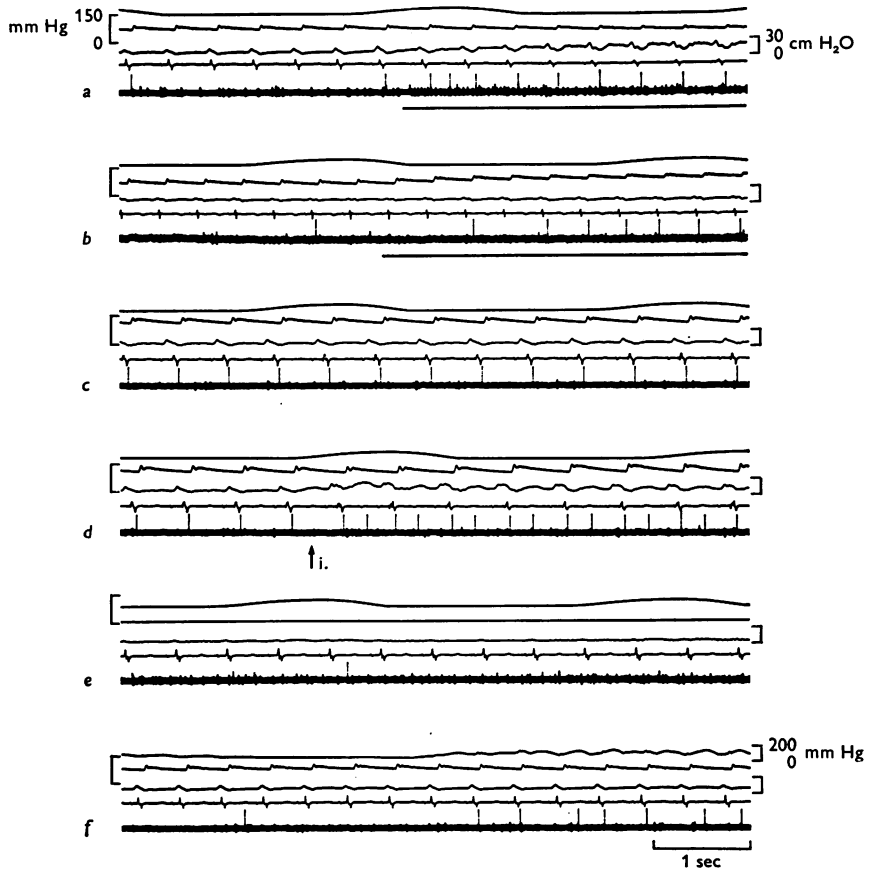

Fig. 2. Activity of a fibre with right ventricular endings. Tracings as in Fig. 1, except for upper tracing in *f* which represents the coronary inflow pressure. *a*, Constriction of the pulmonary artery. *b*, Constriction of the thoracic aorta. *c*, Rise in arterial blood pressure following the intravenous injection of 5 μg noradrenaline. *d*, While the arterial blood pressure is still high, 3 ml. warm saline are injected, beginning at the arrow. *e*, After a bleeding of 55 ml. performed in 6 min. *f*, The coronary flow which has been interrupted 2 sec before, is 0 for the left half of the Figure and is then increased to 19 ml./min as shown by the abrupt rise of coronary pressure.

Effects of various haemodynamic stimuli. Ventricular endings were excited during increases in ventricular pressure. Fig. 2 shows the discharge of a right ventricular fibre during constriction of the pulmonary artery (Fig. 2*a*), constriction of the thoracic aorta (Fig. 2*b*), following the

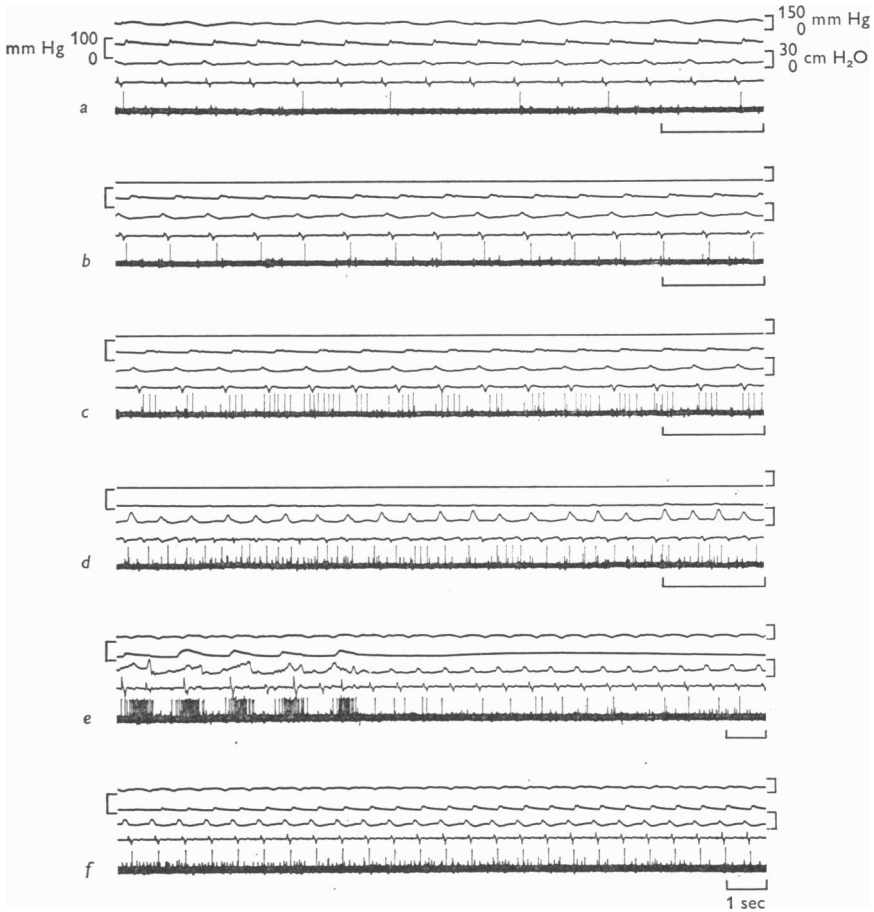

Fig. 3. Effects of a prolonged interruption of left coronary arterial flow. Same fibre with right ventricular endings illustrated in Fig. 2. Tracings as in Fig. 1, except for upper tracings of each record which represent the coronary inflow pressure. *a*, Control (the flow is set at 11 ml./min). *b*, The record starts 70 sec after the coronary perfusion has been interrupted. *c*, Starts 39 sec after the end of the preceding record. *d*, After additional 67 sec; a coarse ventricular fibrillation is present. Fifteen sec after the end of *d* the coronary perfusion is instituted again, however, the ventricles do not contract. *e*, 10 sec later cardiac massages are performed (markedly exciting, mechanically, the endings of the fibre). *f*, Progressively the heart recovers (*e* and *f* are continuous tracings).

I.V. injection of noradrenaline (Fig. 2*c*) and during injection of 3 ml. warm saline (Fig. 2*d*).

The effects of acute bleeding were tested on the activity of three fibres (one from the left and two from the right ventricle). The discharge of each fibre was clearly reduced (as in the example of Fig. 2*e*).

Experiments with perfusion of left coronary artery. Three left atrial fibres, two right ventricular fibres and one left ventricular fibre were studied during perfusion of the left coronary artery.

Brief changes (5–10 sec) in left coronary flow and pressure which did not modify atrial and arterial blood pressures influenced the activity of each fibre. Such activity was decreased when left coronary flow was interrupted and was increased when the flow was resumed (Fig. 2*f*). On the other hand, interruption of left coronary blood flow prolonged enough to produce heart failure (as evidenced by the reduction in systemic blood pressure and the rise in the atrial pressures) excited all of the six fibres.

An example of the increase in neural activity accompanying progressive heart failure, during myocardial ischaemia, is illustrated in Fig. 3. Seventy sec after the coronary pump had been stopped, the fibre discharged more frequently but still very regularly (Fig. 3*b*). Later on, one burst of impulses was present during each cardiac cycle (Fig. 3*c*). When ventricles did not efficiently contract any longer, the discharge of the fibre became irregular (Fig. 3*d*). Coronary flow was then resumed, but cardiac massages, which excited the endings of the fibre, were necessary to stimulate ventricular contraction (Fig. 3*e*).

The mean latency for the excitation of the six fibres during interruptions of left coronary flow was 79 sec. This is comparable to what we reported on afferent cardiac vagal fibres studied in similar conditions (Recordati *et al.* 1971).

The discharge of each of the six fibres was clearly reduced during an acute bleeding (an example is shown in Fig. 2*e*).

The effects of the intracoronary injections of 1–3 μg of veratridine on the activity of a right and of a left ventricular fibre were also tested. Each fibre was excited by the drug 10 and 13 sec, respectively, after veratridine had reached the main coronary artery. Such a long latency preceding the excitation of the endings is comparable to what reported on vagal afferent fibres with ventricular endings (Paintal, 1955).

Similar amounts of veratridine injected in the right atrium had no effect on the activity of the same two fibres.

The conduction velocity of a fibre with left ventricular endings was 13·3 m/sec.

DISCUSSION

Afferent cardiac sympathetic fibres, whose impulse activity was continuously related to normal cardiac events have been described. Since the fibres were dissected from the rami communicantes, they could not represent aberrant vagal fibres.

Location of the receptors. Brown (1964) first reported afferent sympathetic fibres which were excited by mechanical and chemical stimuli affecting the heart. Similar observations were made by Ueda, Uchida & Kamisaka (1969) who studied mainly the effects of direct mechanical stimulations of the beating heart.

We include in this report only fibres whose endings were definitely located in the heart since bursts of discharge were elicited by probing restricted areas of the opened, non-beating heart. This procedure (Coleridge, Hemingway, Holmes & Linden, 1957) is important to distinguish cardiac endings from a variety of thoracic vascular and non-vascular nervous endings (Holmes & Torrance, 1959) which can be affected by mechanical displacements of the beating heart.

For most of the fibres maximal excitation was produced by probing restricted areas of myocardium (0·3–1 cm^2). However, in some cases afferent fibres were excited equally from two distinct but nearby areas, an observation which was already reported for afferent vagal fibres with epicardial receptors (Sleight & Widdicombe, 1965).

We found fibres arising from practically all areas of the atria, auricles and ventricles. Atrial fibres appeared to be equally excited by probing the internal or external surface of the atrium; ventricular fibres were always more excited by probing the internal surface of the ventricle.

If the afferent endings are as widely distributed as our mechanical probing suggests, they may partly correspond to the terminal nervous network or end-nets described by several authors (Meyling, 1953; Holmes, 1957; Miller & Kasahara, 1964; Johnston, 1968). In fact, the auricular appendage may only contain end-nets (Johnston, 1968). Moreover, the end-nets are connected to medullated fibres and do not degenerate after vagal section (Holmes, 1957).

Nature of the stimuli. It is impossible at the moment to decide the mechanical event which mainly regulates the activity of these fibres. In the case of atrial receptors, since their discharge can occur spontaneously during either atrial systole or diastole, it seems likely that they can be excited by both muscular contraction and stretching. The pattern of spontaneous discharge of ventricular receptors suggests that they are mainly sensitive to muscular contraction; however, they are even more

excited when the heart is dilated and weakly beating (as in Fig. 3*c*, *d*, during interruption of left coronary flow).

Comparing the spontaneous activity of these afferent cardiac sympathetic fibres and that of the similarly medullated afferent cardiac vagal fibres (Paintal, 1963), the most obvious difference is that vagal fibres usually show bursts of impulses as opposed to a single impulse, during each cardiac cycle. In order to explain such a difference we advance the hypothesis that the low frequency discharge of the afferent cardiac sympathetic fibres may depend on the transducing properties of their endings, which may be diffuse and thin (e.g. like end-nets).

It is of interest that all of the fibres studied in experiments with coronary perfusion were influenced by changes in left coronary flow and pressure. It is possible that all of the fibres have collaterals which are distributed in or near the coronary vessels (Brown & Malliani, 1971) which would make them sensitive to changes in pressure occurring therein. Another possibility is that changes in coronary perfusion do not act directly on the afferent endings but indirectly through consequent changes in myocardial contractility (Salisbury, 1955; Abel & Reis, 1970; Bacaner, Lioy & Visscher, 1971).

Effects of myocardial ischaemia. All of the fibres studied during interruptions of left coronary blood flow increased their discharge when signs of heart failure were present (decreased systemic blood pressure, increased atrial pressures). Conversely, these fibres had a reduced discharge during acute haemorrhage, although this event is accompanied by a marked decrease in coronary blood flow (Granata, Huvos, Pasqué & Gregg, 1969).

It is likely that the crucial difference between the two situations is represented by the size of the heart which is progressively increased during interruption of coronary flow, but is reduced during acute bleeding (G. Recordati, P. J. Schwartz, M. Pagani, A. Malliani & A. M. Brown, unpublished). Afferent cardiac vagal fibres, studied in similar conditions, showed very similar patterns of responses (Recordati *et al.* 1971). Therefore, sympathetic and vagal cardiac endings, which differ in their spontaneous activity, are both mainly sensitive to mechanical events.

The afferent cardiac sympathetic fibres studied by Brown & Malliani (1971) increased their discharge during myocardial ischaemia after a shorter latency (10–20 sec) and before clear signs of heart failure were present. Those fibres probably represented a different functional population since they were usually either spontaneously silent or they did not discharge in phase with cardiac activity. It is impossible to decide whether those fibres were sensitive to ischaemia *per se* or, more likely, to some earlier mechanical change produced by ischaemia. Unfortunately, those fibres were not studied during acute haemorrhage.

Functional role of the spontaneously active afferent cardiac sympathetic fibres. These fibres are part of an afferent pathway directed to the spinal cord through which spinal (Malliani *et al.* 1969; Brown & Malliani, 1971; Malliani, Pagani, Recordati & Schwartz, 1971; Peterson & Brown, 1971; Malliani, Peterson, Bishop & Brown, 1972) and spino-bulbar (Schwartz, Pagani, Lombardi, Recordati, Malliani & Brown, 1972) reflexes can be elicited.

The present report demonstrates that in such a pathway nervous activity, phasic with cardiac events, is relayed continuously to the central nervous system.

The role of this tonic afferent activity in the neural control of circulation has been overlooked until now.

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