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REFLEX DISCHARGE PATTERNS OF CARDIAC VAGAL EFFERENT FIBRES

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SUMMARY

1. Unit activity was recorded from single and few fibre preparations in a cardiac branch of the right vagus nerve of the cat.

2. Increases in blood pressure mediated solely by the right carotid sinus nerve produced bradycardia when all other nerves to the heart had been cut. Myelinated fibres in the cardiac branch of the right vagus nerve were reflexly activated by the same procedure.

3. The fibres were silent when blood pressure was below 140–150 mm Hg. As the pressure began to rise, they discharged phasically with the cardiac cycle. At pressures greater than 180 mm Hg, the discharge was continuous attaining maximum rates of 40/sec.

4. Stimulation of carotid body chemoreceptors also reflexly excited these fibres, as did stimulation of baroreceptors in both the left carotid sinus and aortic arch. Afferent fibres in the left vagus discharging in response to changes in blood pressure reflexly excited the cardiac efferent fibres. Increases in phrenic motoneurone discharge coincided with inhibition of these fibres. Electrical stimulation of the glossopharyngeal nerve also produced inhibition.

INTRODUCTION

Modification of the output of the cardiac vagi by the activity in the carotid sinus nerves has been known since 1900, but the organization of the connexions between the afferent carotid sinus nerve fibres and the efferent vagal fibres innervating the heart has not been elucidated. Recently, several investigators (Humphrey, 1967; Sampson & Biscoe, 1968; Miura & Reis, 1968, 1969; Seller & Illert, 1969) have traced the afferent input from the carotid sinus nerve through first and second-order synaptic connexions within the medulla, using electrophysiological

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methods. However, because of the numerous connexions made by carotid sinus afferent fibres, it is difficult to specify the nature of a given reflex pathway until the destination of the final central neurone is known. It can be predicted that discharge patterns in the efferent fibres emanating from the final central neurones of a carotid sinus reflex will reflect aspects of its organization such as the number of synapses and the amount of convergence of fibres from other afferent sources.

Along these lines, there are numerous reports of activity of cardiac and 'possible' vagal motor fibres to the heart. Jewett's work in the dog (1964) is the most extensive of these and describes a variety of discharge patterns in primarily cervical vagal units presumed to have a cardiac distribution and in a few fibres of vagal cardiac branches. These fibres (Type I) exhibit certain common characteristics such as pulse modulation and changes in activity opposite to reflex alterations in heart rate. The author reported another type of fibre (Type V), similar to Type I, except that these fibres were either silent during control measurements or fired at a lower frequency than Type I. These reported differences in discharge patterns among fibres may reflect (1) more than one population of fibres innervating the heart, or (2) variation in the influence of the many inputs which converge on the cardiac vagal efferent neurones.

To overcome certain of these ambiguities, a selective approach was used in the present report, concentrating on the discharge patterns of the final central vagal neurones (preganglionic) cardiac vagal fibres, innervating the heart itself. A single input, the right carotid sinus nerve, was used to activate the cardiac vagal centres while other major inputs modulating their activity were controlled or eliminated.

METHODS

A total of sixty-seven successful experiments were done on adult cats. After induction of anaesthesia by ether, the animals were given a mixture of chloralose (40 mg/kg) and urethane (250 mg/kg). For recording arterial pressure, a cannula was inserted into the left femoral artery, passed into the thoracic aorta and connected to a Statham PA23 strain gauge. The rectal temperature was maintained at 37·5° C ± 0·5 using a heated animal board. The animal was artificially ventilated using a positive pressure respirator and end-tidal CO_2 was maintained at 2 % to suppress the activity of phrenic motoneurones. Ribs 1 to 4 were removed on the right side. A cardiac branch of the right vagus nerve was traced to the heart as it passed under the azygos vein. Certain of the small filaments making up this nerve by-passed the heart to innervate the pulmonary vessels and bronchi; care was taken to avoid these filaments during recording.

The cardiac branch was cut as it approached the right atrium, the descending vagus was then cut below it, and dissected back to the neck. The cardiac branch was lifted into a circular container to rest upon a dissecting mirror and was covered with mineral oil to prevent drying. The cardiac branch was divided into small bundles

using fine forceps and sharpened needles, and neural activity recorded from it by lifting one of the small bundles on to a pair of platinum-iridium electrodes. Potentials from the recording electrodes were amplified with a capacity-coupled preamplifier. The preamplifier output was connected in parallel to an auditory monitor, a magnetic tape recorder with an FM electronic recording system, and to the vertical amplifier of an oscilloscope. Unless otherwise stated, the left carotid sinus nerve, the left cervical vagus, and left depressor nerve were cut. The right stellate ganglion was routinely removed, and the T 1–T 5 rami were cut to eliminate activity in sympathetic fibres that join the vagus.

Latency of one reflex pathway was obtained by stimulating the right carotid sinus nerve with a brief pulse (0·2 msec) and recording evoked activity in a single unit in the cardiac vagal branch. To obtain conduction velocities, the same procedure was used with the addition of a pair of stimulating electrodes on the cervical vagus. The stimulus intensity on the cervical vagus was increased until a unit potential was evoked which blocked the response to the carotid sinus nerve stimulation by collision (modified from Paintal, 1953). Conduction velocity was calculated from the delay between stimulus artifact and the evoked response and the distance between stimulating and recording electrodes. When it was not possible to obtain a single unit preparation, bundles of the nerve containing a small number of active units were used.

The impulses in multi-unit recordings were classified according to the spike shapes by an interactive graphics system with a digital computer (Schmittroth in Bessou & Perl, 1969). Additional or special experimental details are given in the Results Section.

RESULTS

The efferent cardiac vagal nerve

To demonstrate that the cardiac vagal nerve chosen for recording actually participated in the carotid sinus reflex, the remaining innervation of the heart was eliminated. The right carotid artery was then occluded for a brief period of time. Release of occlusion was followed by bradycardia and a decrease in pressure. After section of the cardiac vagal branch, bradycardia no longer followed release of carotid artery occlusion.

Innervation of the heart by this branch of the vagus nerve was demonstrated in another way. The right cervical vagus was divided and all other branches below the division were cut. Recording electrodes were placed on the branch before its entrance to the atrium and stimulating electrodes were located on the peripheral side of the divided cervical vagus. Electrical pulses to the cervical vagus (29/sec) at an intensity and duration just subthreshold for C (unmyelinated) fibres evoked cardiac slowing. The electrocardiogram simultaneously recorded showed an increase in the P-P interval, while the P-R interval showed little change. Upon section of the branch near the heart, stimulation of the cervical vagus no longer elicited a decrease in heart rate.

Some characteristics of efferent cardiac vagal units

When recordings were made from the cardiac vagal nerve, efferent units were silent if the systemic arterial pressure was below 140 mm Hg; when arterial pressure was raised above this level by the I.V. injection of epinephrine (3–5 μg/kg) (Fig. 1), saline, or by clamping the descending aorta, they began to discharge.

The vagi and the depressor nerves as well as the carotid sinus nerve contain afferent fibres which reflexly excite efferent units of the vagal cardiac nerve. Fig. 2*A* illustrates efferent activity recorded when both carotid sinus nerves and the aortic (left) depressor nerve were intact. The discharge of these fibres at given levels of systemic arterial pressure was

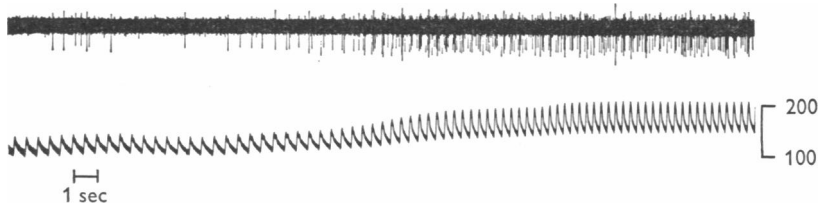

Fig. 1. Response of units in cardiac vagal branch to an increase in systemic pressure produced by epinephrine.

diminished by section of the depressor nerve (Fig. 2*B*), and further decreased after section of the left carotid sinus nerve (Fig. 2*C*); after section of the right carotid sinus nerve, no response remained to an increase in pressure. For this reason, it was concluded that other afferent fibres such as those entering the central nervous system through the spinal cord dorsal roots play only a minor role in activation of the vagal efferent fibres to the heart by increases in arterial pressure. In subsequent experiments, the right carotid sinus nerve alone remained intact, thus limiting the major afferent input of the reflex pathway to this one nerve.

Correlation of efferent cardiac vagal discharge to the cardiac cycle and other features of tonic activity

Low frequency tonic activity was regularly present in the vagal motor fibres responsive to systemic arterial pressure when the mean pressure was between 140 and 180 mm Hg. This tonic activity often had a temporal relation to the cardiac cycle as shown in Fig. 3*A*. The cardiac rhythm was further studied by analysing the pattern of discharge for nine units from seven different preparations having mean arterial pressures ranging from 140 to 160 mm Hg, in each of which the duration of the cardiac cycle remained constant to within 5 msec. Time from peak of aortic pressure pulse to the next discharge of each unit was measured for a number of

cycles (27 or more). In five of the units for which the cardiac cycle was longer than 350 milliseconds (heart rate less than 183), the units discharged between 70 and 400 msec after the peak of the aortic pressure pulse (Fig. 4*A*). With such a great range in the relation between discharge and the previous cardiac systole, it could be expected that when the heart

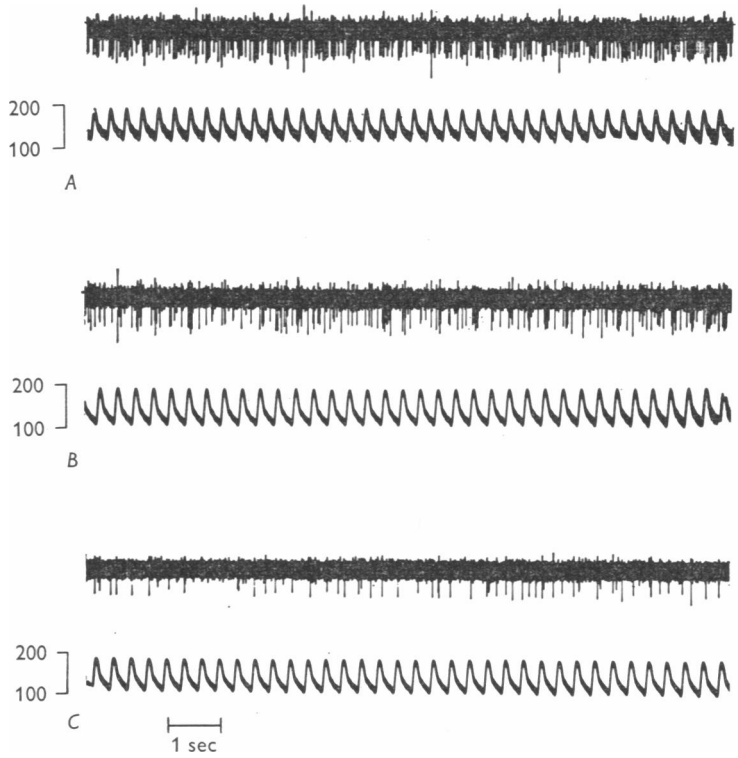

Fig. 2. Activity of cardiac vagal units upon sequential elimination of afferent input from major buffer nerves. *A*: with left depressor, left and right carotid sinus nerves intact. *B*: following section of left depressor nerve. *C*: upon subsequent section of left carotid sinus nerve. After section of right carotid sinus nerve, no activity was seen.

rate was more rapid, efferent impulses with an afferent cardiac rhythm might fall on the early phase of the next cycle. Such was the case for the four units in preparations with cardiac cycles lasting less than 350 msec; in these vagal efferent discharges were observed also during the first 20 msec following the peak of the aortic pressure (Fig. 4*B*). Activity in cervical and/or cardiac vagal motor fibres with a rhythm of discharge related to the cardiac cycle has been previously reported (Jewett, 1962, 1964; Okada, Okamoto & Nisida, 1961*a*, *b*; Iriuchijima & Kumada, 1964;

Katona, Poitras, Barnett & Terry, 1970). Jewett (1964), recording from single efferent fibres in the cervical vagus of the dog, showed that discharge with a cardiac rhythm was most likely to occur between 60 and 240 msec after the beginning of the aortic pulse wave. In his data, the number of impulses in the interval 60–240 msec following the beginning of the aortic pressure wave was statistically greater than in the interval 0–59 msec if the heart rate was less than 200 beats/min. Katona *et al.* (1970) gave comparable results in a preparation similar to that of Jewett.

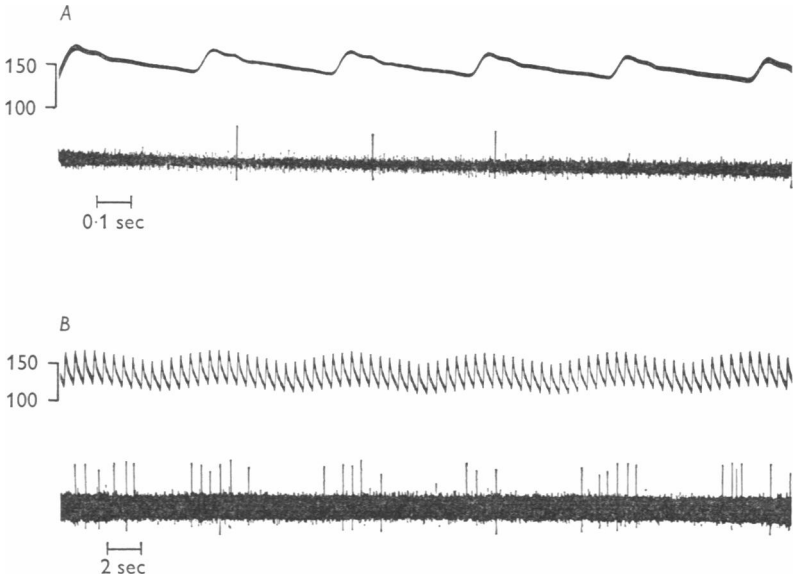

Fig. 3. *A*: relationship of the discharge of cardiac vagal unit to the cardiac cycle. *B*: discharge of cardiac vagal unit occurring during peak of respiratory induced blood pressure fluctuations.

In the present experiments, even those units for which impulses were clearly related to the timing of the cardiac rhythm (arterial pressures between 140 and 160 mm Hg), discharges did not occur during certain cycles (Fig. 3*A*). In other instances, cyclic increases in arterial pressure phasic with respiration unveiled the discharge of a unit related to the cardiac rhythm (Fig. 3*B*).

At mean pressures above 180 mm Hg, most units lost their phasic relation to the heart beat. The frequency of discharge increased as blood pressure rose until a maximum discharge was reached at mean pressures of 200–230 mm Hg. Cardiac vagal efferent units did differ. For example, in one multi-fibre preparation, five units responded at a mean pressure of 210 mm Hg, with maximum frequencies ranging from 5/sec to 35/sec,

indicating substantial differences in response to a given set of conditions. Jewett (1964) also reported a maximum instantaneous frequency of firing of 100/sec by his units after adrenalin, with 30 of 35 fibres reaching levels of 5–30/sec. A somewhat lower maximal instantaneous frequency (40/sec) was seen in the present experiments.

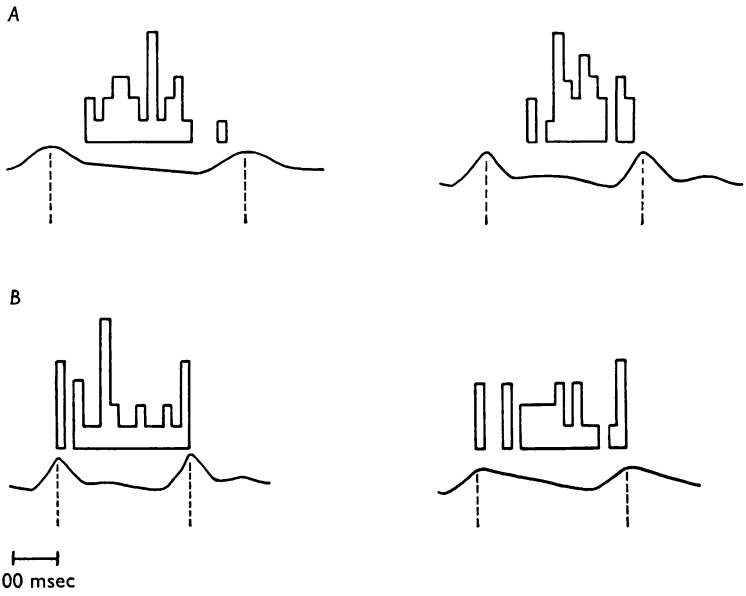

Fig. 4. The distribution of nerve impulses relative to the cardiac cycle for four units. *A*: two units for which cardiac cycle was greater than 350 msec. Discharge did not occur until after the falling phase of the pressure pulse and this continued throughout diastole. *B*: for cardiac cycles less than 350 msec discharge was distributed throughout the cardiac cycle.

Conduction velocity of efferent cardiac vagal fibres

Conduction velocity measured for five efferent cardiac vagal fibres varied between 5·6 and 11·0 m/sec with a mean value of 9·8 m/sec. Jewett (1964) reported conduction velocities of 8·0 and 7·5 m/sec in two cardiac fibres. Iriuchijima & Kumada (1964) using the same method of calculating conduction velocity in cardiac vagal fibres reported a mean value of 8 m/sec (range 4–12 m/sec) for twenty-two fibres. The three sets of results are consistent with values for small diameter myelinated fibres.

Excitation of efferent cardiac vagal fibres by electrical stimulation of the right carotid sinus nerve

Additional information about the reflex pathway was obtained by recording the response of efferent units in the cardiac branch of the vagus to electrical stimulation of the myelinated fibres of the right carotid sinus nerve (monitored by a recording from the nerve itself).

Efferent cardiac vagal units did not respond to stimulation of carotid sinus nerve at low repetition rates (1/sec or less) alone. If, however, a stimulus frequency of 1/sec was preceded by a stimulus frequency of 15–20/sec, single units discharged to the subsequent lower frequency for 1–21 sec before failing to respond. In this way the latency of the reflex response was measured for sixteen units. The value ranged from 26–90 msec with a mean of 51 msec. The distribution of the reflex latencies for the sixteen fibres was unimodal, giving no evidence for different reflex pathways.

Interpretation of the spread of reflex latencies is made difficult by the fact that two types of afferent fibres, chemoreceptors and baroreceptors were included in the stimulation (see below). The variation in the latency of response for a particular vagal unit was as much as 15 msec. Perl (1962), studying the excitation of flexor motoneurones suggested that a monosynaptic input may effectively sum with the varying background level of excitability of a post-synaptic cell to produce discharge for about 1 msec, while polysynaptic excitation of the same elements had much longer periods of summation. Fig. 5 shows the response latency in msec (ordinate) from its first discharge until the unit no longer responded (abscissa) to stimulation of the carotid sinus nerve. The variation in response of the nerve fibres plotted here is too large to be indicative of a monosynaptic response, based upon the somatic motoneurone data. These results, nevertheless, do not rule out a direct connexion between the afferent fibres and the efferent vagal cardiac neurones, since it is not known whether a possible monosynaptic drive to such neurones would have similar durations of action as that observed for somatic motoneurones.

Iriuchijima & Kumada (1963) reported that stimulation of carotid sinus nerve at 1/sec evoked unit activity in cardiac vagal fibres about 60–70 msec after stimulation with considerable fluctuation in the latent period. Their experiments differed in that they did not eliminate the other major baroreceptor inputs. In the present experiments when the left carotid sinus nerve was left intact to provide additional input to the central neurones, stimulation (of the right carotid sinus nerve) at 1/sec alone evoked unit discharge.

An attempt was made to determine whether both the myelinated and

unmyelinated carotid sinus nerve fibres participated in the afferent limb of the reflex. In four experiments, the compound action potential of the carotid sinus nerve was recorded during study of the reflex effects. The response of a group of vagal cardiac fibres to tetanic stimulation of carotid sinus nerve just subthreshold for C fibres is illustrated in Fig. 6*A*. Fig. 6*B* demonstrates how the discharge increased when C fibre impulses

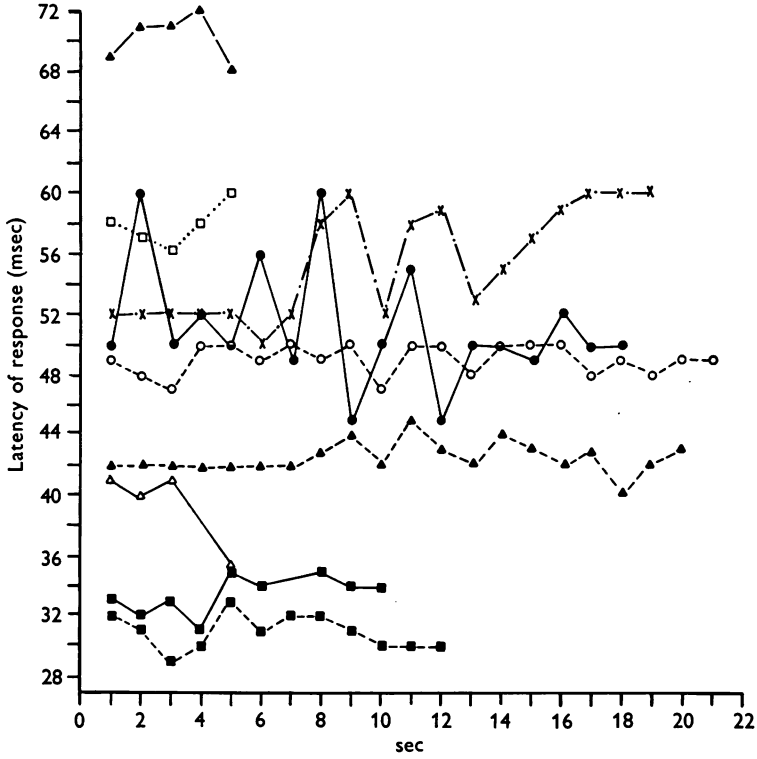

Fig. 5. Graph illustrates variation in latency of response of nine different cardiac units to carotid sinus nerve stimulation. Stimuli were delivered at 1/sec until the unit no longer responded. Unit indicated by — showed the most variation (15 msec) between two stimuli.

were included in the volleys. When the resultant spikes were analysed, for shape and amplitude, two new units were identified in Fig. 6*B*. Furthermore, the study of responses of individual units indicated that one spike, present in both records of Fig. 6, had increased its frequency of firing. Thus, unmyelinated fibres of the carotid sinus nerve have excitatory actions on the same efferent vagal elements as the myelinated fibres of the carotid sinus nerve. The recruitment of additional activity may represent excitatory convergence or it may indicate independent projections.

Influence of carotid body chemoreceptors, respiratory centre, and glosso-pharyngeal afferents on cardiac vagal fibres

Evidence from other investigators suggests that stimulation of the carotid body chemoreceptor produces bradycardia (Heymans, Bouckaert & Dautrebande, 1931; Daly & Scott, 1958; MacLeod & Scott, 1964; Comroe & Mortimer, 1964). Therefore, it was of interest to determine

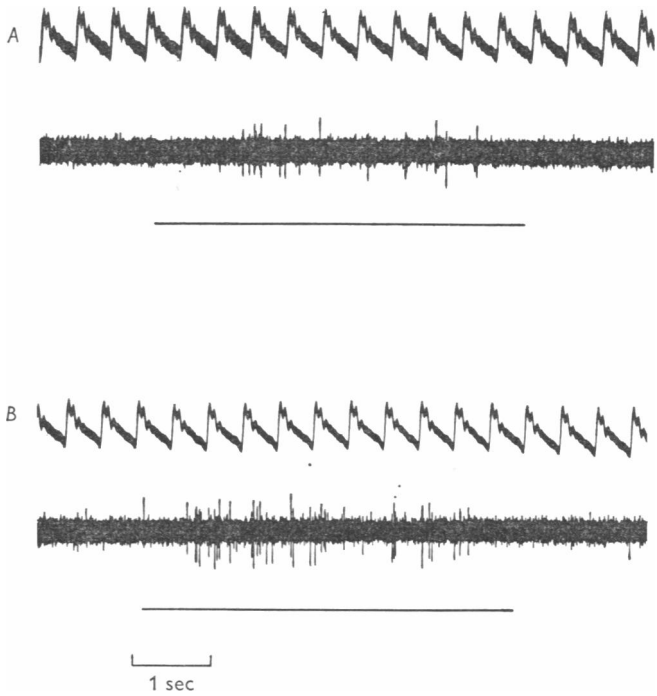

Fig. 6. Discharge of cardiac vagal fibres in response to stimulation of right carotid sinus nerve at 20/sec (indicated by bar). *A*: stimulus was just subthreshold for C-evoked potential of the carotid sinus nerve. *B*: stimulus was maximal for C potential.

whether the same vagal cardiac fibres responded to both arterial pressure changes and chemoreceptor stimulation. Small amounts of cyanide and ACh have been shown to selectively activate chemoreceptor fibres (Landgren, Liljestrand & Zotterman, 1952). Consequently, in four experiments the superior thyroid artery was cannulated to permit injections into the right carotid artery. Five fibres shown to respond to an increase in systemic arterial pressure also responded to injection of 10 μg cyanide or 10 μg ACh. One such unit is illustrated in Fig. 7. On the other hand, not all efferent vagal cardiac fibres were responsive to both efferent stimuli since

thirteen other units in these four experiments responded to increases in systemic arterial pressure, but did not respond to either cyanide or ACh.

Respiratory modulation of vagal activity has been repeatedly observed by other investigators. Classical studies of Anrep, Pascual & Rossler (1935,

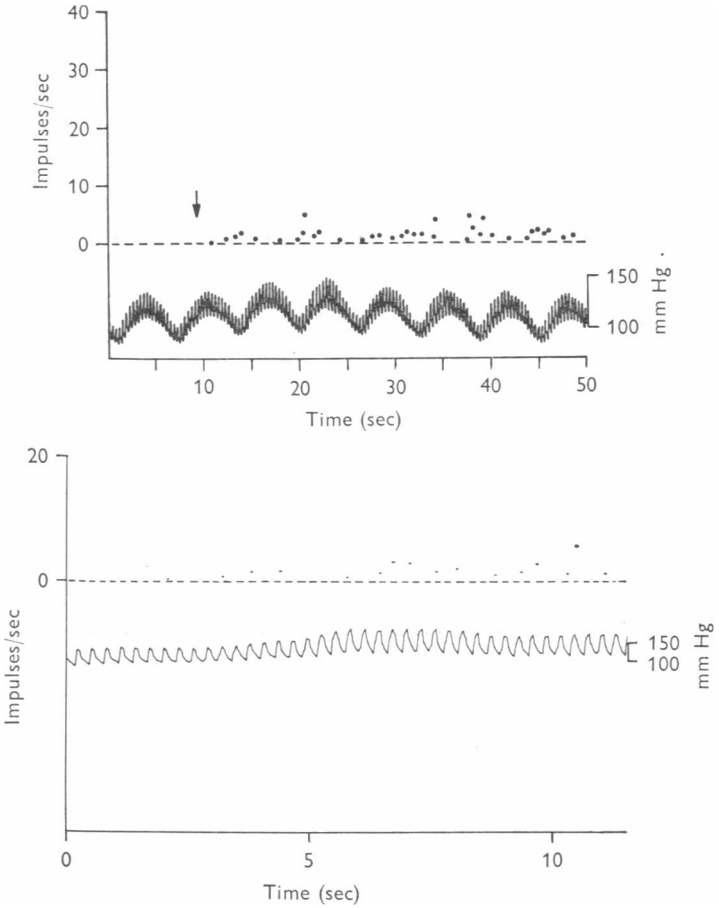

Fig. 7. Response of a cardiac vagal unit. *A*: 10 μg ACh injected into right carotid artery. *B*: increase in blood pressure induced by administration of 5 μg epinephrine. Units were selected on basis of shape from several responding units.

1936) on mechanisms of sinus arrhythmia assigned this modulation to both peripheral and central sources. The peripheral source, namely vagal afferent fibres from the lungs, was eliminated in these experiments by section of non-cardiac branches of the vagi. The central source, central respiratory activity, is influenced by blood levels of CO_2 (Comroe, 1942).

To reduce this latter effect, the preparations were hyperventilated while end-tidal CO_2 was 2% or less. This suppressed central activity of respiratory neurones as judged by the absence of phrenic nerve activity: whenever the CO_2 was allowed to rise above 2%, motor fibres in the phrenic nerve began to discharge. At times when phrenic motor fibres were active, the response of the cardiac vagal units to arterial pressure changes fluctuated with respiration, ordinarily being inhibited during the period of inspiratory activity in the phrenic nerve (Fig. 8).

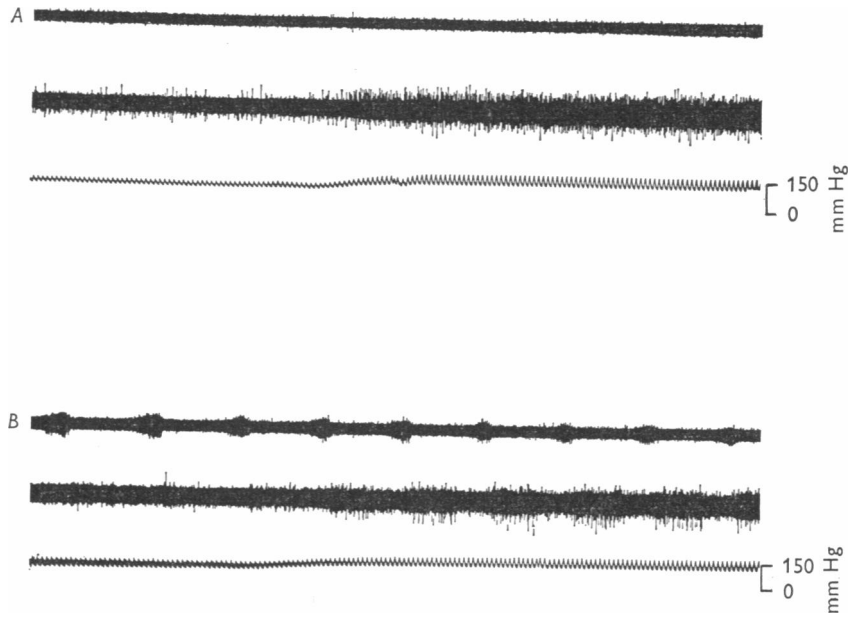

Fig. 8. Discharge of cardiac units in response to blood pressure elevated by injection of 10 μg epinephrine. *A*: animal hyperventilated to end-tidal CO_2 of 2%. Upper trace is recording from phrenic nerve showing almost no activity. Middle trace: discharge of vagal population. Lower trace: systemic arterial pressure. *B*: animal end-tidal CO_2 of 3·5%. Upper trace: phrenic discharge. Middle trace: response of population to B.P. change (lower trace) now shows respiratory modulation.

None of the units in the population studied were excited by stimulation of either glosso-pharyngeal nerve; however, tonically discharging units were inhibited (Fig. 9). Okada, Okamoto & Nisida (1961*a*) reported inhibition of cardiac vagal fibres during swallowing; an inhibition which is lost upon section of both superior laryngeal and the glosso-pharyngeal nerves. It is possible that the inhibitory effect seen in the present work was related to afferent fibres physiologically related to swallowing.

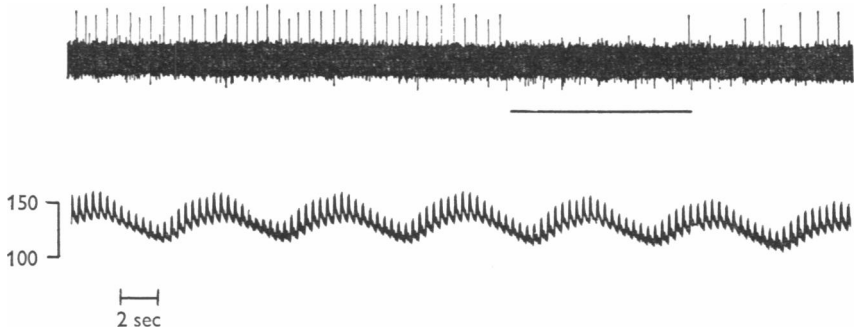

Fig. 9. Tonic activity of vagal unit is inhibited by stimulation of right glossopharyngeal nerve (bar).

DISCUSSION

A population of cardiac vagal efferent fibres is reflexly excited from several afferent sources. The discharge of a single unit, therefore, is a reflexion of the amount of converging activity. When the major source of afferent activity is confined to the right carotid sinus nerve, the efferent discharge reflects the pattern of discharge typical for the carotid sinus input. Fibres of myelinated carotid sinus baroreceptors are not usually active until the blood pressure is above 40–50 mm Hg. At these low pressures, the discharge is maximal during systole, but as the mean pressure increases the impulse frequency in systole and diastole is similar so that the information impinging on cardiovascular centres is more continuous than pulsatile (Bronk & Stella, 1932). All units do not have the same threshold for initial discharge; therefore, more units are recruited as mean pressure increases.

The efferent discharge in the present study resembles the afferent discharge in its cardiac rhythm at lower pressure as well as in its loss of rhythm and increase in frequency at higher pressures. Efferent discharge does not commence at the same levels of blood pressure which initiate activity in the carotid sinus baroreceptors, possibly because more input is necessary to activate the vagal cardiac efferent fibres than is provided by baroreceptors at the lower pressures. Variation in threshold and frequency of discharge seen among the efferent units probably is a reflexion of similar variations in the afferent discharge. To make quantitative statements interpreting the vagal cardiac discharge patterns in light of the carotid sinus input, it would be necessary to control the parameters of input pressures systematically. In the work described in this report, most observations of unit activity were made when the various parameters of blood pressure were not controlled.

As expected (Hoff, 1955), excitation of fibres in the branch appear to have more of an influence on the sino-atrial node than on the atrio-ventricular node because activation was accompanied by definite changes in the P-P interval of the ECG but not by changes in the P-R interval. Whether activity in the efferent fibres also initiates a change in atrial contractility was not determined.

The location of the soma of cardiac vagal motoneurones was thought to be the dorsal motor nucleus of the vagus (Kosaka, 1909). The studies of Calaresu & Pearce (1965*a*, *b*) and Kerr (1969) indicate that areas other than this nucleus are primarily responsible for vagal cardiac control. The constancy of the responsive patterns in this study suggests that an analysis of discharge patterns evoked in central neurones by similar inputs could provide clues on the central organization of the reflex pathways and more precisely identify the neurones taking part in them.

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