J. Physiol. (1975), **245**, *pp.* 699–712
With 10 *text-figures*
Printed in Great Britain

BARORECEPTOR AND CHEMORECEPTOR INFLUENCES ON HEART RATE DURING THE RESPIRATORY CYCLE IN THE DOG

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(*Received 22 July 1974*)

SUMMARY

1. Brief stimuli were delivered to the carotid chemoreceptors or baroreceptors in dogs anaesthetized with pentobarbitone or chloralose. Chemoreceptor stimulation was achieved by rapid retrograde injections of 0·2–0·5 ml. warmed, CO_2-equilibrated saline through a cannula in the external carotid artery. Baroreceptor stimulation was achieved by forceful retrograde injection of 2–5 ml. air-equilibrated saline, or of freshly drawn arterial blood, into the external carotid artery after first clamping the common carotid artery.

2. Brief baroreceptor stimuli had no noticeable effect on breathing. Brief chemoreceptor stimuli had no effect on breathing in some dogs, but in many produced a reflex increase in the depth of inspiration when delivered during inspiration. In these same dogs, brief chemoreceptor stimuli delivered in expiration either prolonged the expiratory pause or evoked an active expiratory effort.

3. Prompt decreases in heart rate were elicited by brief sudden chemoreceptor or baroreceptor stimuli when these were delivered during the expiratory phase of respiration. The stimuli did not modify the control heart rate pattern when delivered during inspiration. If the carotid sinus nerve or the vagus nerves were cut the responses were abolished.

4. Brief chemoreceptor or baroreceptor stimuli remained effective in evoking prompt decreases in heart rate during periods of apnoea in the end-inspiratory position (Hering–Breuer inflation reflex). In periods of apnoea after prolonged artificial hyperventilation the stimuli were sometimes ineffective at first, but were always effective late in the period of apnoea, again producing prompt cardiac slowing.

5. After denervation of the lungs, brief baroreceptor and chemoreceptor stimuli continued to evoke prompt falls in heart rate when given during

expiration. When delivered during inspiration the same stimuli were either ineffective, or less effective.

INTRODUCTION

Stimulation of the carotid sinus baroreceptors is well known to cause a reflex bradycardia (e.g. Hering, 1927). Stimulation of the carotid arterial chemoreceptors also causes a primary reflex bradycardia, although this may be obscured or reversed by secondary effects due to the stimulation of breathing (Daly & Scott, 1958).

Experiments on cats have established that when a brief stimulus is delivered to the carotid chemoreceptors during an inspiration, the depth of that inspiration is reflexly increased. When a similar stimulus is delivered during the expiratory phase of a respiratory cycle, it has little effect, or simply prolongs the expiratory pause (Black & Torrance, 1971; Eldridge, 1972). The effects upon the heart rate of similar stimuli to the chemoreceptors, and of brief stimuli to the carotid baroreceptors, were investigated here in anaesthetized dogs. We found that such stimuli cause prompt reflex slowing of the heart when they are delivered during expiration, but are without effect upon the heart rate when delivered during inspiration.

Part of this work has been reported in brief form (Haymet & McCloskey, 1974).

METHODS

Experiments were performed on twenty-five adult dogs of both sexes weighing from 5 to 12 kg. The animals were anaesthetized with (i) I.V. or I.P. pentobarbitone (Nembutal: Abbott: 35 mg/kg: eight dogs), or (ii) I.V. thiopentone (Pentothal: Abbott: 25 mg/kg), followed by I.V. chloralose (α- chloralose: British Drug Houses: 80 mg/kg: seventeen dogs). Eight dogs (four of each above category) were given a supplemental dose of morphine (1–2 mg/kg I.V.) early in the period of anaesthesia before the experimental procedures. In each dog the trachea was cannulated low in the neck, and nylon cannulae were inserted, with their tips pointing towards the heart, into the lingual and external carotid arteries on one or both sides. On each side the tips of these cannulae were positioned close to each other and in close communication with the carotid sinus. A nylon cannula was inserted into the right external jugular vein and advanced so that its tip lay within the thorax in or near the right atrium. Rectal temperature was kept between 37 and 39° C.

Arterial pressure was recorded from a lingual artery using a Statham P23AC transducer. Right atrial pressure was recorded through the jugular venous cannula using a similar transducer. Both pressures were recorded on a Grass Polygraph pen recorder. On another channel of the recorder either the electrocardiogram or the heart rate was recorded using a Grass 5P4D pre-amplifier. Respiration was recorded on the fourth channel of the polygraph. Usually this was achieved by the bag-in-box method similar to that described by Donald & Christie (1949) in which the animal inspired through a valve from a bag enclosed in an airtight box into which expired

air was led: pressure in the box was measured using a Grass PT5A volumetric pressure transducer. Alternatively, respiratory movements of the chest were recorded from tension changes produced through an elastic band sewn to the chest wall and connected to a Grass FTO3 force transducer (cf. Levy, DeGeest & Zieske, 1966).

Brief chemoreceptor stimuli were delivered by the sudden retrograde injections into an external carotid artery of small volumes (0·2–0·5 ml.) of warmed, physiological saline through which 100 % CO_2 had been bubbled (CO_2 saline: cf. Black & Torrance, 1971; Eldridge, 1972). These injections produced only slight transient alterations, if any, in carotid sinus pressure as measured from the lingual artery.

Brief baroreceptor stimuli were delivered by the sudden retrograde injection into an external carotid artery of a larger volume (2–5 ml.) of warmed, air-equilibrated, physiological saline, after first clamping the common carotid artery. Prior to these injections the carotid sinus pressure was reduced below systemic arterial pressure by 25–75 mmHg because of the common carotid arterial occlusion. Usually the sinus pressure remained pulsatile, presumably because of open anastomotic channels. At the injection of saline the carotid sinus pressure rose by 50–150 mmHg, and then fell back to its initial control level, the whole change taking about 1 sec to complete. On some occasions freshly drawn arterial blood was re-injected instead of saline.

In three dogs anaesthetized with pentobarbitone, recordings were made from single afferent fibres in the cut carotid sinus nerve (four chemoreceptors and seven baroreceptors) during the manoeuvres described above. These recordings were made using stainless steel electrodes, and the impulses were amplified on a Tektronix 122 pre-amplifier and recorded on a Y.E.W. ultra-violet recorder with galvanometers giving a flat frequency response to 1000 Hz. Injections of 0·2–0·5 ml. CO_2 saline set up intense short-lasting (1–4 sec) volleys of impulses in chemoreceptor fibres, but had almost no effect upon the discharges of baroreceptor fibres. Injections of larger volumes of air-equilibrated saline, or of arterial blood, after clipping the common carotid artery, set up intense volleys of impulses in baroreceptor fibres, lasting as long as the carotid sinus pressure disturbances, but had no effect upon chemoreceptor afferent discharge (see Fig. 1).

RESULTS

(i) *Effects upon breathing.* Brief baroreceptor stimuli had no noticeable effect on breathing. Brief chemoreceptor stimuli delivered during an inspiration reflexly increased the depth of that inspiration in fourteen of the twenty-five dogs. In the same animals, brief chemoreceptor stimuli delivered early in an expiration either prolonged the expiratory pause (five dogs) or caused an active expiratory effort (nine dogs). Stimuli delivered late in the expiratory phase evoked an inspiratory effort in these animals. These findings are similar to those reported by Black & Torrance (1971) and by Eldridge (1972) for the cat, except that those authors did not see active expiratory efforts in response to stimuli given in expiration. Active responses to inspiratory and expiratory stimuli are shown in Fig. 2. In the remaining eleven of the twenty-five dogs investigated, including seven of the eight dogs given morphine, brief chemoreceptor

stimuli evoked no respiratory responses. In three dogs the carotid sinus nerve was cut on the experimental side: in all three this abolished active responses to inspiratory and expiratory chemoreceptor stimuli.

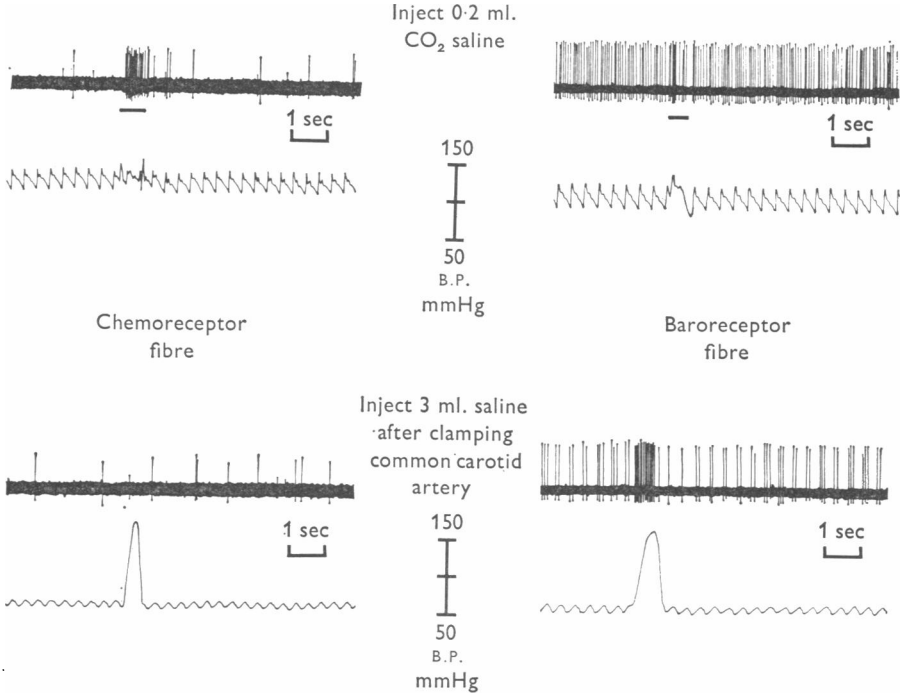

Fig. 1. Dog. Pentobarbitone. Chemoreceptor afferent activity (left panels) and baroreceptor afferent activity (right panels), recorded from filaments dissected from the carotid sinus nerve, are shown together with records of blood pressure simultaneously recorded from near the carotid bifurcation. The effects on both forms of activity of injection into the carotid bifurcation of 0·2 ml. CO_2-equilibrated saline are shown in the top two panels. The effects of forceful injection of 3 ml. air-equilibrated saline into the carotid sinus, after first occluding the common carotid artery, are shown in the lower two panels (neural activity records retouched).

(ii) *Effects upon heart rate.* Brief chemoreceptor or baroreceptor stimuli delivered during expiration caused a prompt and brief decrease in heart rate. When delivered during inspiration similar stimuli either failed to alter heart rate, or failed to modify a control pattern of sinus arrhythmia when this was present. The decreases in heart rate which could be evoked during the expiratory phases of breathing could no longer be evoked after the carotid sinus nerve was cut on the experimental side (three dogs), or after bilateral vagotomy (five dogs), or after intravenous administration of atropine (1·2 mg, three dogs).

Responses to brief chemoreceptor stimuli are shown in Fig. 2. When 0·1–0·2 ml. of air-equilibrated saline was injected instead of a similar volume of CO_2-saline, no effects upon heart rate were observed.

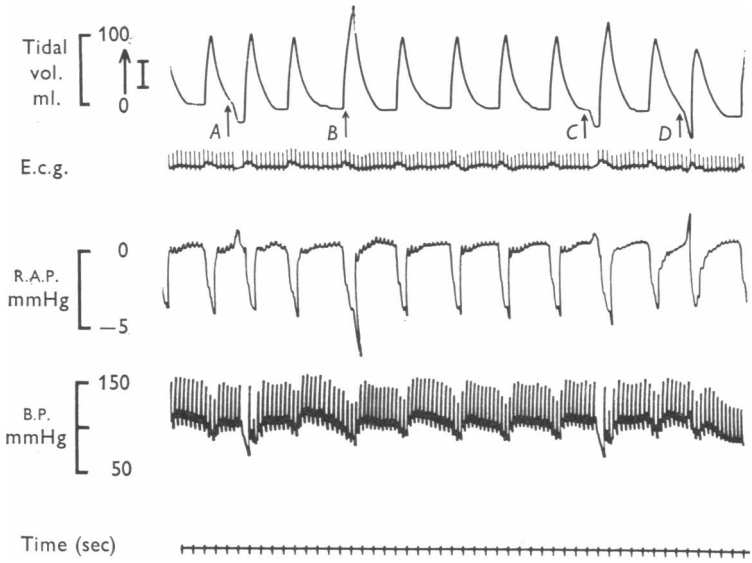

Fig. 2. Dog. Chloralose. Records of tidal volume (inspiration upwards), electrocardiogram, right atrial pressure, and arterial pressure are shown. At *A*, *B* and *C* injections of CO_2-saline were made into the carotid bifurcation to provide brief chemoreceptor stimulation. When these stimuli were delivered in expiration (*A* and *C*), they evoked a prompt slowing of the heart, and an expiratory effort. When the stimuli were delivered in inspiration (*B*), they evoked an increased inspiratory effort but no change in heart rate. As a control, the chest was squeezed at *D* to mimic the thoracic and atrial pressure changes seen with the chemoreceptor stimuli given in expiration, but this did not affect heart rate.

Responses to brief baroreceptor stimuli are shown in Fig. 3. Frequently the baroreceptor stimuli evoked less dramatic alterations in heart rate than did the chemoreceptor stimuli chosen. The phase of the respiratory cycle during which baroreceptor stimuli were effective in evoking a reflex bradycardia commenced after the peak of inspiration and during expiratory air flow, and lasted through the expiratory pause until the commencement of the next inspiration. This is shown in Fig. 3. The phase of the respiratory cycle during which chemoreceptor stimuli were effective was similar, although the chemoreceptor stimuli also altered the respiratory cycle so that no two cycles were alike during alterations in timing of such stimuli. We were unable to demonstrate any relation between the magnitude of the heart rate response and timing of the stimuli within the expiratory phase.

(iii) *Effects of lung and thoracic volumes upon heart rate responses.* From the observations reported above it appeared to us that some event associated with inspiration is capable of making the vagal centres completely or partly refractory to afferent inputs from arterial baroreceptors or chemoreceptors. One obvious possible event is the physical expansion of

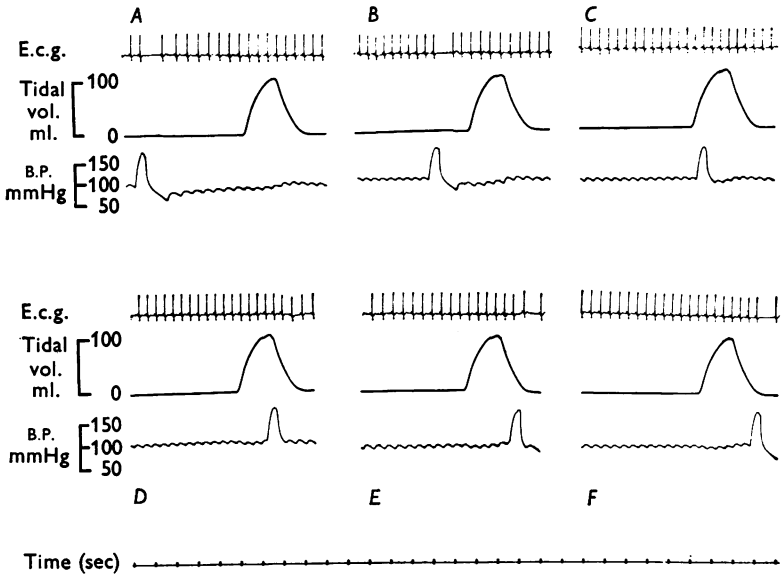

Fig. 3. Dog. Chloralose and morphine. Records of electrocardiogram, tidal volume and carotid sinus blood pressure are shown. Baroreceptor stimuli were timed to occur at various points in the respiratory cycle. Stimuli occurring during the expiratory pause (*A*, *B* and *F*), or during expiratory air flow (*E*), produced prompt cardiac slowing. Stimuli given during inspiration (*C* and *D*) did not slow the heart.

the lungs and thorax which would, of course, be associated with the activation of numerous pulmonary and thoracic mechanoreceptors. In order to investigate this possibility, we gave brief stimuli to the baroreceptors or chemoreceptors during periods of apnoea evoked by the Hering–Breuer inflation reflex. This reflex was called into play by occluding the expiratory line so that the animals' lungs remained inflated at normal end-inspiratory volume. During the ensuing period of respiratory arrest the usual brief baroreceptor or chemoreceptor stimuli remained effective in producing reflex bradycardia (see Figs. 4 and 5). Often the stimuli appeared less effective during the inflation reflex, as illustrated in Figs. 4 and 5, but the responses were still quite marked. In other animals the bradycardia evoked by brief stimuli given during the inflation reflex was extreme, and much

more pronounced than the slowing evoked during the expiratory phases of breathing. In the example shown in Fig. 6, which is not the most dramatic response we have seen, the heart stopped for over 7 sec in response to a brief chemoreceptor stimulus given during the inflation reflex.

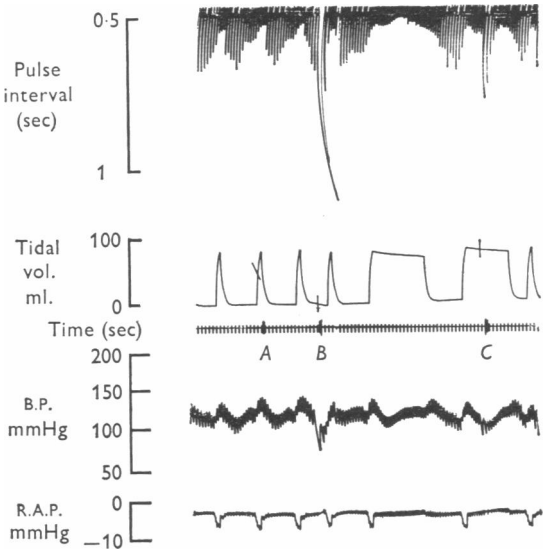

Fig. 4. Dog. Pentobarbitone. Records of pulse interval, tidal volume, carotid sinus blood pressure and right atrial pressure are shown. On two occasions the expiratory line was occluded so that the animal was held at his end-inspiratory position. At the marks *A*, *B* and *C* brief chemoreceptor stimuli were delivered into the carotid bifurcation. Stimuli given in inspiration (*A*) evoked no heart rate responses. Stimuli given in expiration (*B*), and stimuli given during inspiratory apnoea (*C*), evoked prompt cardiac slowing.

We also made a different approach to the question of whether changes in the volumes of thorax or lungs are the important phasic events which determine the effectiveness of baroreceptor and chemoreceptor stimuli in slowing the heart. In this we artificially hyperventilated dogs so that they would remain apnoeic for over 1 min upon cessation of pumping. In these animals the lungs could be left passively deflated, or else inflated to any chosen degree during the period of apnoea. Chemoreceptor or baroreceptor stimuli were typically ineffective upon heart rate early in such periods of apnoea, regardless of the degree of lung inflation, but became effective later in the period of apnoea. This was seen repeatedly in experiments on five dogs, the results from one of which are shown in Fig. 7.

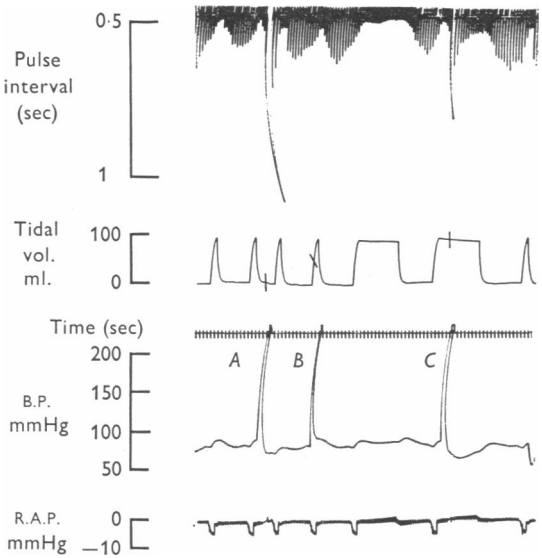

Fig. 5. Dog. Pentobarbitone. Records of pulse interval, tidal volume, carotid sinus blood pressure and right atrial pressure are shown. On two occasions the expiratory line was occluded so that the animal was held at his end-inspiratory position. At the marks *A*, *B* and *C* brief baroreceptor stimuli were delivered. Stimuli given in inspiration (*B*) evoked no heart rate responses. Stimuli given in expiration (*A*), and stimuli given during inspiratory apnoea (*C*), evoked prompt cardiac slowing.

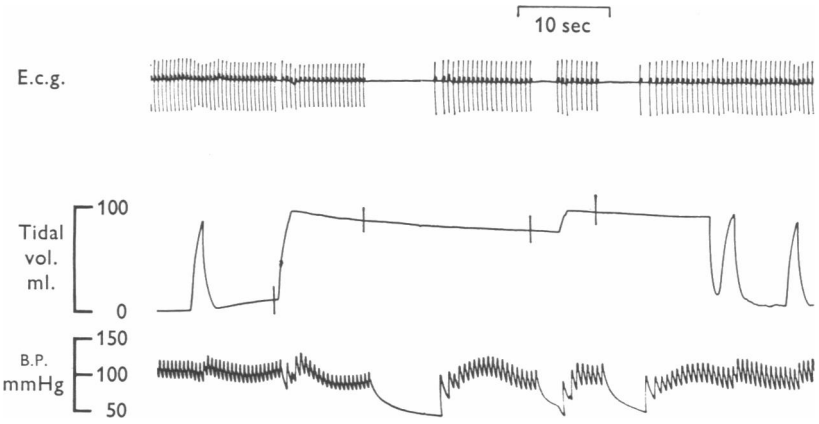

Fig. 6. Dog. Pentobarbitone. Records of electrocardiogram, tidal volume and carotid sinus blood pressure are shown. At the marks on the respiratory record brief chemoreceptor stimuli were delivered within the carotid sinus. After the first such stimulus the expiratory line was occluded and produced inspiratory apnoea. After the third stimulus the animal made a further inspiratory effort, and then became apnoeic again. All stimuli evoked prompt falls in heart rate.

When stimuli were delivered during a period of continuing artificial hyperventilation they were usually ineffective regardless of the phase of the imposed cycle in which they were given. We found that only when the respiratory pump was adjusted so that the animal was making occasional spontaneous respiratory efforts did the stimuli slow the heart. On these occasions the effectiveness of the stimuli was related to the phase of these spontaneous respiratory efforts in the same way as during control periods of spontaneous breathing.

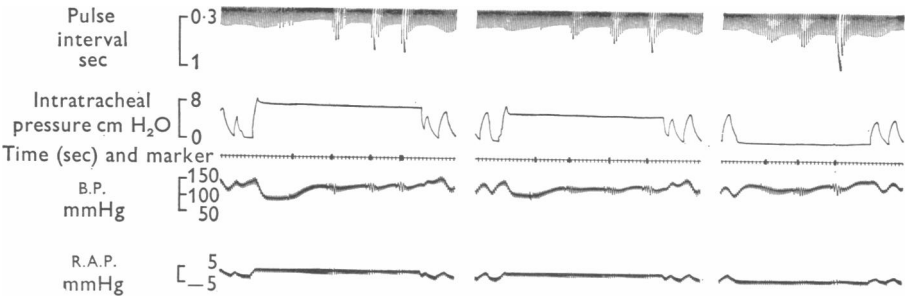

Fig. 7. Dog. Chloralose. Records of pulse interval, intratracheal pressure, carotid sinus pressure and right atrial pressure are shown. Each segment of record is taken in a period of apnoea after at least 2 min of artificial hyperventilation. Brief chemoreceptor stimuli were delivered into the carotid bifurcation where indicated by the stimulus marker. Stimuli delivered late in the period of apnoea were more effective in evoking falls in heart rate.

(iv) *Effects of denervation of the lungs.* In six dogs the lungs were denervated. This was done, on the right-hand side, by opening the chest through the fourth intercostal space and cutting the vagus close to the hilum of the lung. The vagosympathetic trunk was cut also below the hilum of the lung. This is the method used by Daly & Scott (1958) to denervate the lungs without interrupting cardiac vagal branches. The chest was closed, the pneumothorax reduced, and spontaneous breathing re-established. On the left-hand side the vagus was cut in the neck. Evidence for successful pulmonary denervation was that no sign of a Hering-Breuer inflation reflex remained after the denervation procedure, even when the lungs were grossly over-inflated. The resting heart rates after denervation, however, were little altered from their control values prior to the thoracotomy.

Brief stimuli delivered to the arterial baroreceptors or chemoreceptors after pulmonary denervation evoked a prompt bradycardia when delivered during expiration in all six dogs. In three dogs, similar stimuli were

ineffective when delivered during inspiration (see Fig. 8). In the other three dogs, slight falls in heart rate were evoked by such stimuli given during inspiration: in these the increases in pulse interval produced by inspiratory stimuli of either type were always smaller than those produced by similar stimuli given during expiration. The results from these three dogs are summarized in Fig. 9. No changes in heart rate could be evoked by our stimuli in any of the six dogs after cutting the right vagosympathetic trunk in the neck.

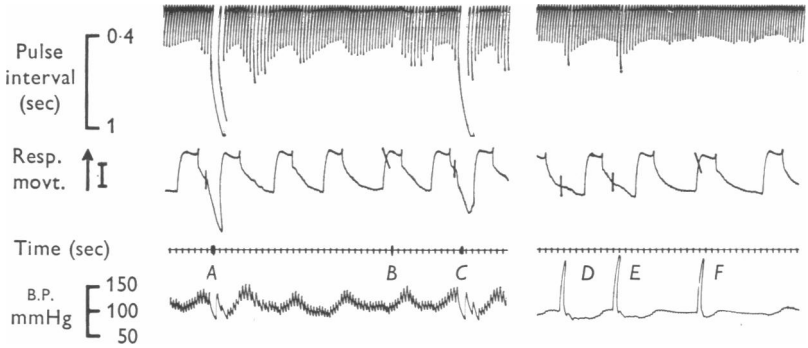

Fig. 8. Dog. Chloralose. Pulmonary vagi cut. Records of pulse interval, respiratory movements (inspiration upwards) and carotid sinus pressure are shown. Brief chemoreceptor stimuli were given at *A*, *B* and *C*, and brief baroreceptor stimuli at *D*, *E* and *F*. Stimuli given in inspiration (*B*, *F*) did not affect heart rate. Stimuli given in expiration (*A*, *C*, *D*, *E*) evoked prompt falls in heart rate.

(v) *Heart rate and the respiratory cycle.* Brief intense stimuli of the type described above do not occur in nature. The phenomenon of respiratory modulation of vagal efferent effects on the heart may still, however, manifest itself when the intense baroreceptor or chemoreceptor stimulation is sustained. Schweitzer (1937) noted that conspicuous sinus arrhythmia developed in response to a sustained increase in carotid sinus pressure, and Levy *et al.* (1966) found a similar response to a sustained hypoxic stimulus presented to the isolated carotid body. While these authors did not draw attention to it, it appears from their records that the sinus arrhythmia they saw was produced by a cardiac slowing confined almost entirely to the expiratory phase of the respiratory cycle. This would fit well with the findings we have reported. A similar phenomenon can be simply demonstrated by occluding the trachea of a dog at the end of a normal expiration (see Fig. 10). As asphyxia develops and blood pressure rises, bradycardia develops, and is clearly most pronounced in expiration.

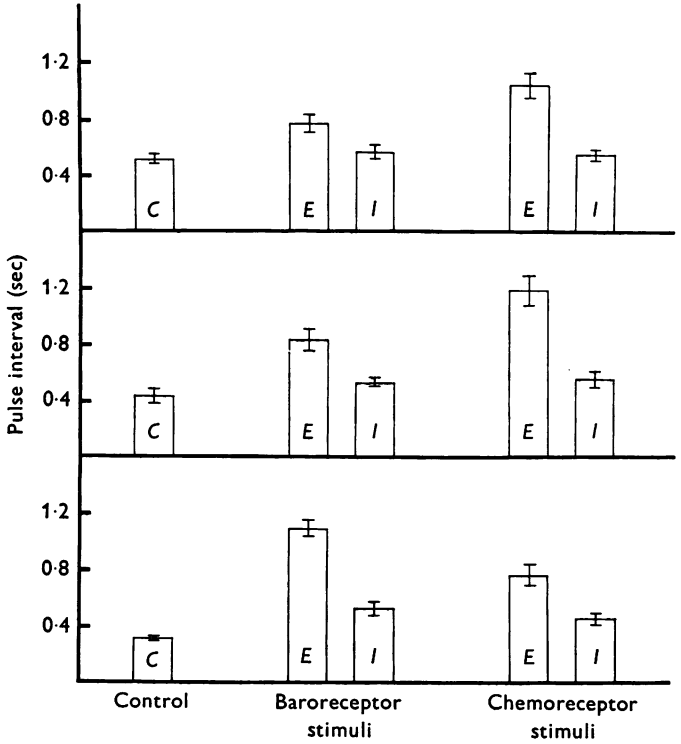

Fig. 9. Data from three dogs anaesthetized with chloralose, and with their pulmonary vagi cut, are shown. For each dog the pulse interval in the control condition (*c*) is shown. The greatest responses to baroreceptor stimuli or chemoreceptor stimuli delivered during expiration (*E*) or inspiration (*I*) are shown for each animal. The height of each panel shows the mean pulse interval, and the bars give ± 2 S.E. of mean, for ten intervals.

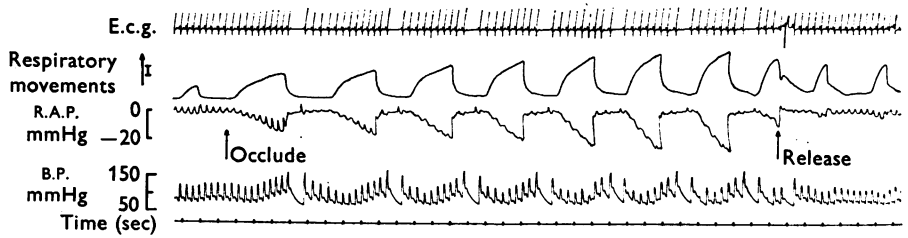

Fig. 10. Dog. Chloralose. Records of electrocardiogram, respiratory movements, right atrial pressure and carotid sinus pressure are shown. At the first arrow the airway of the animal was occluded with the lungs and thorax in the normal end-expiratory position. At the second arrow this occlusion was released. Note that bradycardia developed, and was confined almost entirely to the expiratory phase of the respiratory cycle.

DISCUSSION

This study indicates that cardio-inhibitory vagal efferent mechanisms are rendered wholly or partly refractory to excitatory afferent inputs from arterial baroreceptors or chemoreceptors during the inspiratory phase of the respiratory cycle.

The refractoriness of the vagal mechanisms is not entirely caused by the activation, during inspiration, of slowly adapting mechanoreceptors in the thorax or lungs because it does not persist during maintained inflation either in the Hering–Breuer inflation reflex or during periods of apnoea following hyperventilation. Nor is the phasic refractoriness abolished by pulmonary denervation. However, some participation of intrapulmonary or thoracic receptors, particularly of a rapidly adapting kind, cannot be ruled out by our experiments.

A consistent association in our observations exists between the activity of the inspiratory centres and the refractoriness of the efferent vagal mechanisms. When inspiratory centres are active, even after pulmonary denervation, the refractoriness is present. When the inspiratory centres can be presumed to be inactive, as in the Hering–Breuer inflation reflex, then the refractoriness is absent. Some activity in the respiratory centres is probably necessary, however, for our stimuli to be effective in evoking reflex bradycardia. In periods of apnoea following hyperventilation in our study, such stimuli were at first ineffective, at which times probably little activity was present in the respiratory centres. Later in the periods of apnoea, however, when some activity of the respiratory centres may have begun at a low level, the stimuli became effective (see Fig. 7). It might be preferable, therefore, to regard our results as indicating that expiratory centre activity renders the vagal efferent mechanisms accessible to baroreceptor and chemoreceptor stimuli, rather than that inspiratory centre activity renders them refractory to these stimuli.

Iriuchijima & Kumada (1964) showed that impulses could be evoked in vagal efferent nerve fibres in the dog by electrical stimulation of the central cut end of the carotid sinus nerve, and that such responses were more reliably evoked by stimuli delivered during expiration than during inspiration. Those stimuli probably excited both baroreceptor and chemoreceptor afferents. Our experiments confirm their findings and show that discharges from either receptor type have similar effects. On some occasions Iriuchijima & Kumada were able to evoke vagal responses by stimuli delivered during inspiration, indicating that the inspiratory refractoriness of the vagal mechanisms is not absolute.

Biscoe & Sampson (1970) found that the discharge of phrenic motoneurones could be inhibited by the stimulation of carotid baroreceptors

with brief pulses of pressure similar to those used here. It is therefore surprising that we observed no ventilatory responses to baroreceptor stimulation. It is possible that small respiratory influences would be more reliably detected by phrenic nerve recording than by the less sensitive measurements of ventilation employed here, so that very slight respiratory effects were not detected in this study.

Boushey, Richardson, Widdicombe & Wise (1974) have shown that CO_2 can excite laryngeal afferent nerves. It is conceivable that the CO_2-saline injections given in our experiments may have spread to arteries supplying the larynx and produced reflex effects through their action on laryngeal receptors. This is suggested particularly by our demonstration of active expiratory responses in some dogs, because expiratory efforts are not a usual feature of the carotid body reflex but might be accounted for by a laryngeal reflex (i.e. cough). This possibility was excluded here for those experiments in which the carotid sinus nerve on the experimental side was cut, abolishing both respiratory and heart rate responses to the CO_2-saline stimuli. Moreover, in our first four experiments in this series a more extensive dissection was done than was later found necessary: in these experiments the pharynx and larynx were removed in a block dissected from just above the sternum up to the level of the hyoid bone. In all four experiments typical heart rate responses were evoked as we have described, and in two there were active inspiratory and expiratory responses to the chemoreceptor stimuli.

Black & Torrance (1971) found that brief chemoreceptor stimuli effectively increase ventilation if delivered in inspiration. We have made similar findings in the dog, and find in addition that such stimuli effectively evoke bradycardia only if delivered in expiration. Black & Torrance observed that the prompt responses of the chemoreceptors which would enable them to 'follow' normal oscillations of arterial gas tensions could have importance in respiratory control. They noted that the circulatory time lag from pulmonary capillaries to carotid bodies delays the presentation of the oscillating blood gas stimuli to the receptors. If this time lag could be altered, then the rising phase of chemoreceptor discharge could be made to alter its timing in relation to the respiratory activity which is proceeding. In exercise, for example, the rising phase of discharge might be shifted by a more rapid circulation from coincidence with expiration to coincidence with inspiration, and so provide a more effective ventilatory stimulus. Our results allow this interesting hypothesis to be extended. It would be expected that a shift in phase between chemoreceptor responses and breathing which favoured respiratory stimulation would minimize the reflex bradycardia, and a shift which minimized respiratory stimulation would favour reflex bradycardia. Such alterations would seem

appropriate in exercise, for example, if Black & Torrance's suggestions were correct.

The phenomenon we have described is essentially a modulation imposed by the respiratory system upon the cardiovascular system, and is likely to require consideration in a number of situations. Clearly it may contribute importantly in sinus arrhythmia. In general, whenever there is an alteration in respiratory activity, the effectiveness of baroreceptor and chemoreceptor reflexes mediated through the vagus can be expected to be changed.

This work was supported by grants from the National Heart Foundation of Australia and the Australian Research Grants Committee. B.T.H. was a Vacation Scholar of the National Heart Foundation of Australia.

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