REGULATION OF RESPIRATION BY BRONCHOPULMONARY RECEPTORS IN CONSCIOUS DOGS

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Abstract. In awake dogs, the Hering-Breuer inflation reflex (HBIR) was present but weaker than during anaesthesia. Auditory or visual distraction, increased body temperature, and exercise decreased or abolished HBIR. Bilateral complete vagal blockade resulted in slow deep breathing, but arterial PCO_2 and apnoeic threshold PCO_2 were unaffected. Vagal blockade decreased the response of frequency of respiration during hypoxemia and hypercapnia, but did not affect the response to increasing body temperature or to exercise. Progressive cooling of the exteriorized vagal loops from 16 to 9°C resulted in progressive abolition of HBIR, but the respiratory response to inhaled histamine was unaffected. There was a decrease in the expiratory phase of respiration and in tidal volume; the dogs hyperventilated at rest and had an increased respiratory response to inhaled CO_2. Further cooling of the vagal loops sufficient to abolish the respiratory response to inhaled histamine resulted in the slow, deep breathing pattern and impaired respiratory frequency response to inhaled CO_2 typical of the completely vagotomized animal.

INTRODUCTION

Although the vagus nerves are the afferent pathway for various respiratory reflexes that affect the rate and depth of breathing, it is not known what influences specific reflexes exert on the control of normal breathing. Furthermore, most studies of ventilatory control have been performed during anaesthesia, which may affect various areas of the nervous system differently, and ventilatory responses to some stimuli (e.g., exercise) cannot be studied during anaesthesia. Therefore, we have developed techniques to study ventilation in awake dogs and to compare

them with studies performed during anaesthesia. We have exteriorized the cervical vagi to make them accessible for blockade, and have designed copper radiators to fit snugly around the exteriorized vagal skin loops to cool the vagus nerves to different temperatures in order to block differentially various reflexes. The detailed results of these studies are reported separately (Phillipson et al. 1970, 1971, 1972, Fishman et al. 1971).

METHODS

We trained six dogs (weight, 20–29 kg) to stand quietly in place. We performed a permanent tracheostomy in each dog, exteriorized cervical portions of both vago-sympathetic nerve trunks in loops of skin (Phillipson et al. 1971), and allowed at least one month for healing and training.

During the ventilatory studies, the dogs breathed through a cuffed endotracheal tube (inner diameter, 1.0 or 1.3 cm) inserted through the tracheostomy and attached to a Lloyd valve (dead space, 24 ml).

We sampled tracheal gas through an infra-red CO_2 analyzer (Beckman LB-1) from the records of which we calculated end-expired (alveolar) CO_2 tension. The CO_2 analyzer was calibrated with gases of known composition immediately before and after each series of measurements, and the CO_2 sampling line was heated to body temperature. Expired gas was collected in a Tissot spirometer for measurement of minute volume of ventilation and calculation of tidal volume. All variables were recorded on a Beckman Type R Dynograph recorder.

The ventilatory response to hypercapnia was determined by a steady-state method (Phillipson et al. 1970). Inspired gases containing 2–7% CO_2 in air were administered through the Lloyd valve. Measurements of minute volume of ventilation, respiratory frequency, and tidal volume were made for 2–3 min beginning 8 min after a steady end-expired CO_2 tension was obtained.

The ventilatory response to hypoxaemia was determined by having the dogs breathe 10% O_2 (Phillipson et al. 1970). To this gas mixture we added CO_2 in sufficient concentration to maintain the end-expired CO_2 tension at the level that was present for the 8 min before the dog breathed the hypoxic gas. The response to hypoxaemia was determined 1–3 min after the dog began breathing the 10% O_2 mixture.

The ventilatory response to exercise was determined by having the dogs run on the treadmill at speeds of 1.5–4.0 mph for at least 8 min at each speed (Phillipson et al. 1970). We avoided the problem of panting during exercise by using only mild-to-moderate treadmill speeds and by

maintaining a cool environment (laboratory temperature, 21–23°C). For studies on the ventilatory response to hyperthermia the dogs were heated by allowing the room temperature to increase.

The Hering–Breuer inflation reflex was elicited by inflating the lungs during inspiration to a pre-set tracheal pressure of 5–25 cm water (Phillipson et al. 1971b). The duration of apnoea elicited by the reflex was measured as the period of time from lung inflation to the first inspiratory effort, indicated by an abrupt decrease in tracheal pressure. Airway pressure was measured continuously with a Statham P23Db strain gauge.

In the studies of arterial blood gases, we inserted a cannula into one carotid artery to allow sampling of blood for gas tensions and pH. A temperature probe (Yellow Springs Instrument Co., No. 511) was placed in the carotid artery through the cannula for measurement of arterial temperature. Arterial blood CO_2 tension, O_2 tension, and pH were measured with Radiometer electrodes at 37°C, and the results were corrected to blood temperature with a blood gas calculator.

The apnoeic threshold arterial CO_2 tension was determined with the dog standing on the treadmill (Phillipson et al. 1970). We hyperventilated the dog's lungs with 100% O_2 (using an intermittent positive-pressure ventilator) to produce various steady levels of arterial hypocapnia. After 8 min at a given arterial CO_2 tension, the ventilator was turned off and the duration of time to the first breath was noted. The arterial CO_2 tension which just produced apnoea was taken as the apnoeic threshold level.

In the experiments in which we blocked the vagus nerves completely, we did so by injecting 3–5 mg of tetracaine into each vagal loop with the dog standing quietly on the treadmill (Phillipson et al. 1970). Tourniquets were placed around each end of the loop for 20–30 min to minimize systemic absorption of the anaesthetic. By this method vagal blockade was achieved for 6–8 hr as judged by the following criteria: tachycardia equal to or greater than that produced by 1 mg of atropine administered intravenously on another occasion; a change in the pattern of breathing to slow, deep respirations; abolition of the Hering-Breuer inflation reflex; and the presence of Horner's syndrome.

In the experiments with differential cooling of the cervical vagus nerves, we cooled both vagus nerves by circulating cold water through copper radiators constructed to fit snugly around the vagal skin loops (Fishman et al. 1971). We measured the temperature of the water continuously at the outflow port of the radiators with thermistors, and we maintained the temperature constant to within ±0.2°C in each radiator. We first made control steady-state measurements, and then cooled the

vagal loops to a present temperature and waited 15–30 min after establishing a new steady-state before measuring the variables again.

To detect the presence of intact bronchopulmonary irritant receptors, we administered histamine diphosphate (4% in 0.9% sodium chloride) by aerosol (in a D-30 nebulizer) intratracheally (Sellick and Widdicombe 1971).

RESULTS

Effects of general anaesthesia

Since most studies concerning the role of vagal reflexes in the control of breathing have been performed during anaesthesia, we attempted to study how some vagal regulatory mechanisms differed in awake dogs.

Hering-Breuer inflation reflex. In 18 studies performed on 3 awake dogs, the duration of apnoea elicited by the Hering-Breuer inflation reflex varied with the inflating pressure (5–25 cm H_2O) (Fig. 1). The
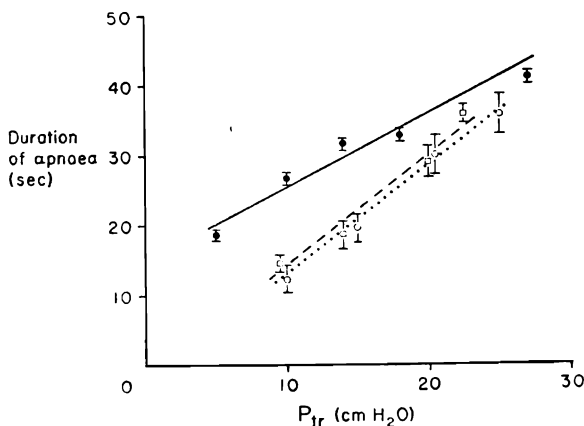

Fig. 1. Relationship between inflating pressure in the trachea (P_{tr}), and duration of apnoea elicited by Hering-Breuer inflation reflex. Dogs standing on treadmill. Data points are means of 4–8 determinations $\pm$ standard deviations. Filled circles, Dog 1; open circles, Dog 2; open squares, Dog 3. (From Phillipson et al. 1971.)

duration of apnoea was reproducible to within ± 3 sec during a single study and to within ± 5 sec from day to day for a period up to 18 months. In each of two dogs, general anaesthesia with either sodium pentobarbitone or halothane increased the duration of apnoea elicited by the Hering–Breuer inflation reflex compared with the same dogs in the conscious state (Fig. 2).

When one vagus nerve was blocked by injecting local anaesthetic into

either vagal loop in the unanaesthetized dogs, the Hering–Breuer inflation reflex was abolished. Blockade of one cervical vagus nerve in the same dogs during general anaesthesia decreased the duration of apnoea but did not abolish the reflex (Fig. 2). Thus, in the awake state, there appears to be central multiplication of the effects of impulses arising in the two vagi, since blockade of one vagus nerve completely abolished the reflex. The finding of bilateral evoked potentials within the medulla by afferent impulses from each vagus nerve (Anderson and Berry 1956, Porter 1963)
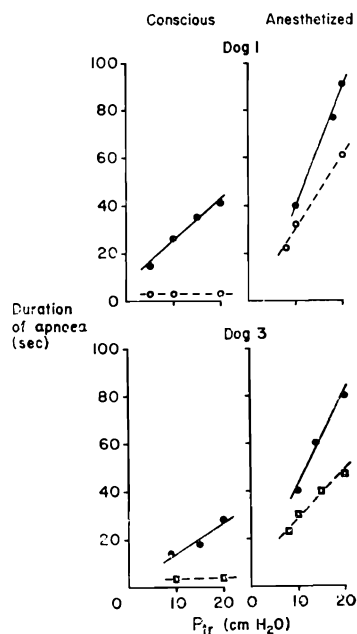

Fig. 2. Effect of general anaesthesia on duration of apnoea elicited by Hering–Breuer inflation reflex. P_{tr}, intratracheal pressure used to inflate lungs; filled circles, vagi intact; open circles, left vagus blocked (Dog 1); open squares, right vagus blocked (Dog 3). Dog 1 anaesthetized with halothane; Dog 3 anaesthetized with sodium pentobarbitane. (From Phillipson et al. 1971)

supports the possibility that central multiplication may occur. Since anaesthesia potentiates the Hering–Breuer inflation reflex and results in loss of central multiplication of information from both vagi relating to this reflex, conclusions based on studies in anaesthetized dogs of the Hering–Breuer inflation reflex and its role in the regulation of breathing may be misleading when applied of the conscious animal.

Alveolar ventilation. In each of three conscious dogs studied on two occasions, bilateral vagal blockade by injection of local anaesthetic into both vagal loops had no significant effect on arterial CO_2 tension or on apnoeic threshold CO_2 tension, although tidal volume increased and respiratory frequency decreased (Phillipson et al. 1970). These findings differ from results in anaesthetized dogs (Lim et al. 1958, Honda et al. 1962, Pleschka et al. 1966) in which vagotomy produced a decrease in arterial

CO_2 tension and in apnoeic threshold CO_2 tension. General anaesthesia may depress the forebrain to a greater degree than the medullary centres (Redgate 1963) resulting in a relative increase in the influence of vagal input on the "respiratory centres", and this difference may explain our findings. Thus, studies performed during anaesthesia cannot be applied to the awake animal.

Medullopontine vs. higher central nervous system regulation of respiration

We attempted to determine the role of the vagus nerves on the response to various stimuli known to affect respiration at different levels of the central nervous system.

Hering–Breuer inflation reflex. In each of three awake dogs, the Hering–Breuer inflation reflex was elicited within the normal tidal volume range. This reflex differs from that in unanaesthetized man (Guz et al. 1964), perhaps because impulses arising from cerebral centres above the medulla have a dominant influence on the "respiratory centres" in man (Euler et al. 1970). In our awake dogs, we had to minimize auditory and visual distraction in order to demonstrate reproducibly the Hering–Breuer inflation reflex. With increasing body temperature, the duration of the Hering–Breuer inflation reflex decreased progressively. At the point of panting, the Hering–Breuer inflation reflex could no longer be elicited. Thus, in awake dogs, vagal influences are modified markedly by stimulation of higher central nervous centres. During exercise, the duration of apnoea elicited by the reflex decreased as the work rate increased, suggesting that under these conditions the vagus nerves have a decreasing influence on respiration.

Effect of vagal blockade on the respiratory response to various stimuli. In three awake dogs, bilateral vagal blockade with a local anaesthetic decreased the response of minute volume of respiration to hypercapnia (Fig. 3), primarily due to failure to increase respiratory frequency. These findings are similar to those obtained in conscious rabbits (Richardson and Widdicombe 1969). In each of three awake dogs, bilateral vagal blockade decreased the response of minute volume of ventilation during hypoxaemia; respiratory frequency did not increase significantly (Fig. 4). However, vagal blockade did not prevent the response of minute volume of ventilation or of respiratory frequency to increasing arterial temperature (Fig. 5), suggesting that the role of the vagus nerves is most important in modulating respiratory input at the medullopontine level, rather than in higher central nervous centres (e.g., hypothalamus). In each of eight studies on three awake dogs, the response of minute volume of ventilation to exercise was unaffected by bilateral vagal blockade (Fig. 6).
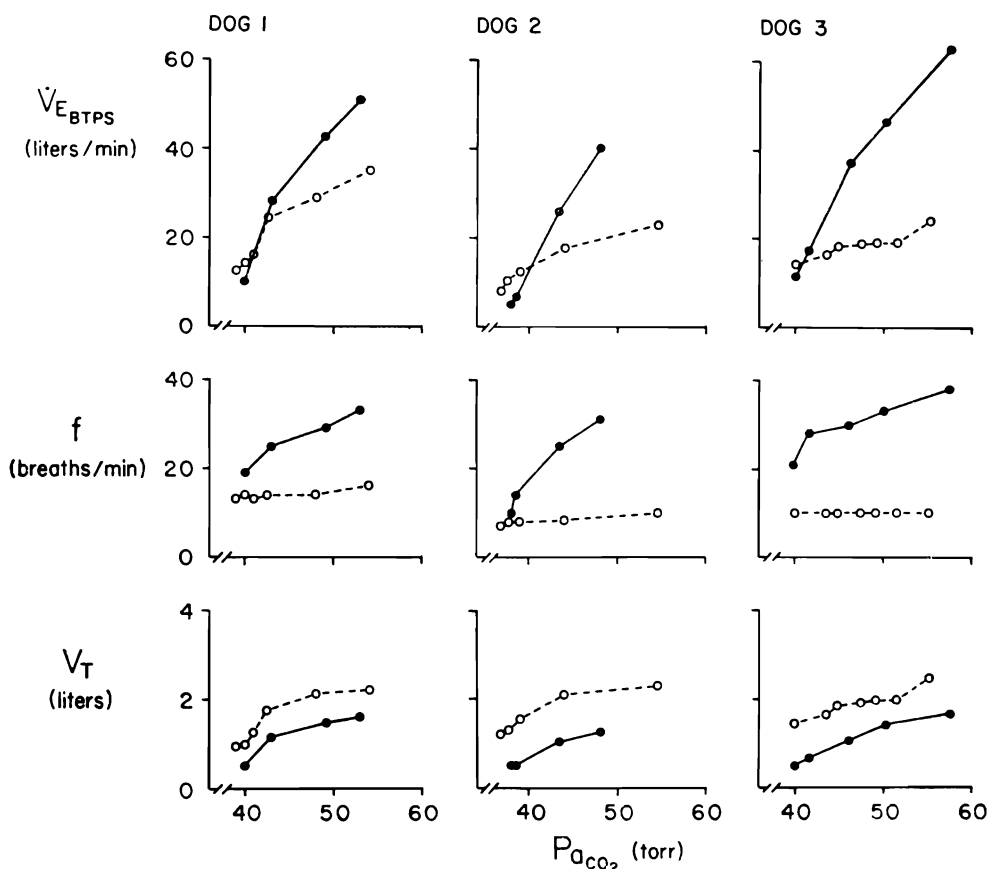
Fig. 3. Effect of blockade of both cervical vagus nerves on the response of minute volume of ventilation ($\dot{V}_E$), respiratory frequency (f), and tidal volume (V_T) to increasing arterial CO_2 tension ($PaCO_2$). Dog 2, standing on treadmill; Dogs 1 and 3, walking at 2 mph. Filled circles, vagi intact; open circles, vagi blocked. (From Phillipson et al. 1970.)

Respiratory frequency was lower at each level of exercise during vagal blockade, but increased significantly with increasing work rate (Fig. 6). Thus, the respiratory response to exercise does not appear to be modulated primarily by vagal influences.

Receptors responsible for control of rate and tidal volume in awake dogs

Since complete bilateral vagotomy in awake dogs resulted in slow, deep breathing and abolished the response of respiratory frequency to hypercapnia and hypoxaemia, it is obvious that vagal influences play a role in the normal regulation of respiratory rate and tidal volume in
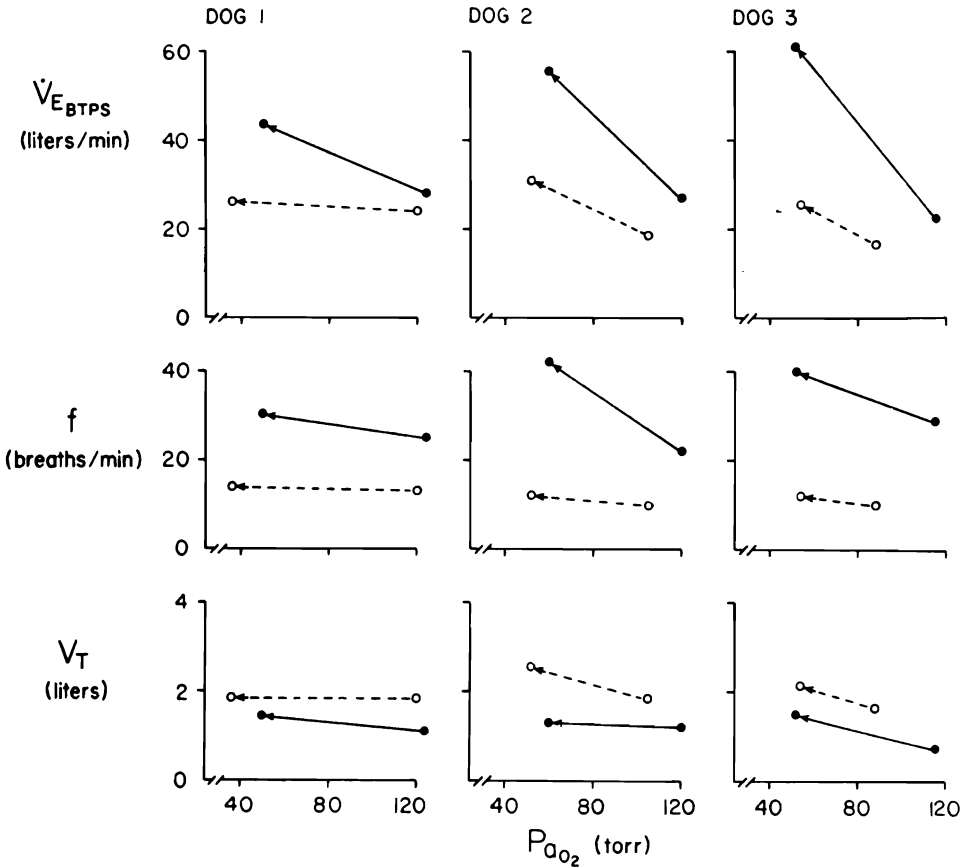
Fig. 4. Effect of blockade of both cervical vagus nerves on the response of minute volume of ventilation ($\dot{V}_E$), respiratory frequency (f), and tidal volume (V_T) to decreased arterial O_2 tension (PaO_2) at a constant, slightly elevated arterial CO_2 tension ($PaCO_2$: Dog 1, 43 torr; Dog 2, 42 torr; Dog 3, 43 torr). Filled circles, vagi intact; open circles, vagi blocked. (From Phillipson et al. 1970.)

these animals. Furthermore, transient inflation of the lungs inhibited inspiration (presumably by stimulation of slowly adapting receptors) and inhalation of histamine aerosol caused rapid, shallow breathing (presumably by stimulation of irritant receptors) (DeKock et al. 1966, Sellick and Widdicombe 1971). Therefore, it was logical to attempt to study the relationship between these respiratory reflexes and normal ventilation by attempting to block these reflexes separately. We considered the use of anodal block, but discarded it for the following reasons: (i) This technique blocks conduction in myelinated fibres of the cervical vagus nerves and leaves the non-myelinated fibres functioning (Guz and Trenchard 1971). Since the J-receptors are the only lung receptors known to have

Fig. 5. Effect of blockade of both cervical vagus nerves on the response of minute volume of ventilation ($\dot{V}_E$), respiratory frequency (f), and tidal volume (V_T) to increasing arterial temperature. Dog walking at 2 mph. Filled circles, vagi intact; open circles, vagi blocked. (From Phillipson et al. 1970.)
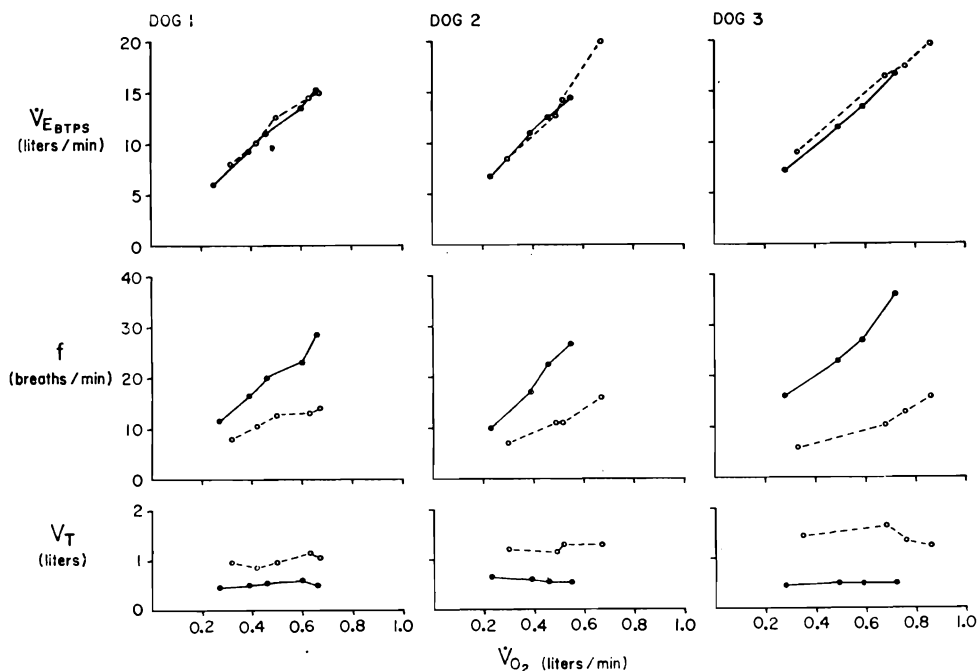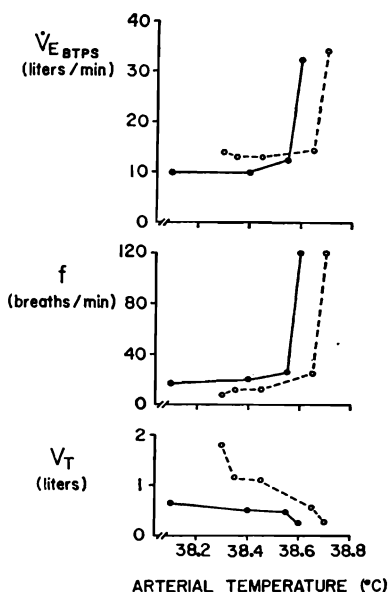
Fig. 6. Effect of blockade of both cervical vagus nerves on the response of minute volume of ventilation ($\dot{V}_E$), respiratory frequency (f), and tidal volume (V_T) to increasing levels of exercise (expressed as oxygen consumption, $\dot{V}O_2$). Filled circles, vagi intact; open circles, vagi blocked. (From Phillipson et al. 1970.)

non-myelinated fibres, and since these receptors do not appear to be involved in the normal control of breathing (Guz and Trenchard 1971), this approach did not appear promising for our purposes. (ii) We could not adapt this technique of block to unanaesthetized animals.

Cooling the exteriorized nerves is another technique for blocking nervous conduction differentially. We were able to construct copper radiators which fit snugly around the vagal skin loops so the segments could be cooled. We ruled out the possibility that cooling the skin itself had an effect on respiration by demonstrating that placement of the cooled radiators directly on the shaved neck of the dog did not alter the respiratory pattern. However, the differential cooling technique has major limitations: (i) It has been shown that the maximum frequency of discharge that can pass unblocked through a region of cooled nerve decreases with progressive cooling, so that low frequency discharges may be transmitted while high frequency discharges are not (Paintal 1966). Therefore, it is probably not possible to block completely conduction of impulses from slowly adapting receptors without altering conduction of impulses from some irritant receptors. (ii) There are low and high threshold slowly adapting receptors and their fibre responses to cooling differ (Paintal 1966). (iii) The thermistor measured the temperature of the surface of the cooled skin loop, not the nerve itself. The temperature of the nerve must have been somewhat higher than the skin loop, depending on the blood flow through the skin. Therefore, we used the temperatures to give a reflection of the differential cooling, rather than as an exact measure of temperature of the nerve istelf. Nevertheless, the temperature measurements were very useful because respiratory responses were reproducible from day to day at a given temperature. Our approach was to attempt to block reflex responses (rather than single fibres) separately and to correlated these with alterations in spontaneous breathing patterns. By regulating the temperature in the cooling thermodes carefully, we were able to abolish the Hering–Breuer inflation reflex progressively without blocking or reducing the ventilatory response to histamine aerosol. By this means, we were able to separate different components of the respiratory pattern.

In 27 studies on three awake dogs, the duration of apnoea elicited by the Hering–Breuer inflation reflex decreased progressively as the vagi were cooled below a radiator temperature of 16°C (Fig. 7). During this first phase of vagal cooling there were several associated changes in respiration: (i) The most striking alteration in respiratory pattern that occurred during progressive blockade of the Hering–Breuer inflation reflex was a marked and linear decrease in the expiratory phase of respiration (Fig. 7). (ii) There was acceleration of the early expiratory

phase of respiration, associated with visible expiratory effort of the dog's abdominal muscles. (iii) The duration of inspiration either did not change or increased only slightly. (iv) There was no increase in tidal volume, and in fact there was a significant decrease over the range of radiator temperatures from 16 to 9°C (Fig. 7). (v) Inhalation of aerosolized histamine still resulted in rapid, shallow breathing, indicating that the reflex
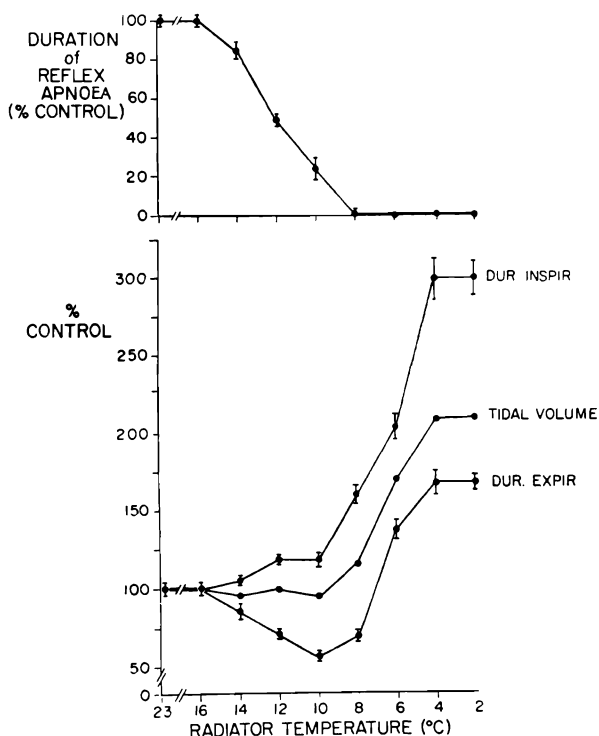

Fig. 7. Effect of progressive cooling of the exteriorized vagal loops on the duration of apnoea produced by inflating the lungs (tracheal pressure, 20 cm H_2O), the duration of inspiration (dur. insp.), the duration of expiration (dur. expir.) and the tidal volume in one dog. Data (mean and standard error) of 10 consecutive breaths are expressed as a percentage of the control values with the vagal loops warm. Tidal volume is reported as the mean measured over 1 min.

response of irritant receptors was not blocked. In fact, the ventilatory response to inhaled histamine aerosol was greater than in the control state with the vagi warm. (vi) There was an increase in the minute volume of ventilation compared to the control state before cooling, and a significant decrease in end-expired CO_2 tension (range, 2–4 mm Hg). (vii) The steady-state ventilatory response to inspired CO_2 was increased above the control state.

After the Hering–Breuer inflation reflex was abolished and the vagus nerves were cooled further (until the respiratory response to inhaled histamine was abolished), we found the following effects on respiration (Fig. 7): (i) The duration of expiration increased to levels above the control state with the vagi warm. (ii) The duration of inspiration increased. (iii) Tidal volume increased. Respiration now was identical with the slow, deep breathing pattern that occurred with complete blockade of the vagus nerves with local anaesthetic. (iv) The alveolar CO_2 tension returned to normal. (v) There was a decreased response of minute volume of ventilation and no increase in frequency during hypercapnia, similar to the results obtained with local anaesthetic blockade of the vagus nerves.

These studies indicate that the vagus nerves have more than one effect on respiration, and that these effects can be distinguished by cooling the nerves to different temperatures. At higher temperatures (16 to 9°C) the Hering–Breuer inflation reflex was progressively abolished but the ventilatory response of an irritant stimulus was unimpaired. We do not suggest that all conduction was blocked in fibres from slowly conducting receptors or that all fibres conducting from irritant receptors were intact, but only that sufficient bursts were blocked to abolish the response of one reflex and insufficient blockade occurred to inhibit the other response. At these temperatures, the most significant effect on the respiratory pattern was a decrease in the expiratory period. These findings suggest that the firing of receptors responsible for the Hering–Breuer inflation reflex are also a determinant of the expiratory period. We have other physiologic evidence that information coming from the lungs during inspiration has a delayed effect on the time of the next inspiration: when the lungs of awake dogs are inflated transiently at the time of a normal inspiration, but to a larger tidal volume (even with added CO_2) and allowed to deflate immediately, the next inspiratory effort is diminished. Since bursts of activity from slowly adapting receptors during lung inflation occur only during inspiration, how could the activity from these receptors affect the next inspiration? One possible explanation is that sufficient volleys of these impulses may cause prolonged hyperpolarization of medullary or pontine inspiratory units, requiring a longer period for these cells to return to a firing threshold.

Vagal influences responsible for inhibiting inspiration and thereby limiting tidal volume must be different from those described above, since tidal volume did not increase when the vagus nerves were cooled to temperatures sufficient to abolish the Hering–Breuer inflation reflex and to decrease the expiratory period progressively. Further cooling of the nerves (and presumably blockade of more impulses) was required

before the slow, deep breathing pattern typical of the vagotomized animal occurred. Several receptors must be considered for the role of inspiration-inhibition. J-receptors have been described, but previous studies suggest that they do not play an important role in the normal control of breathing (Guz and Trenchard 1971). Furthermore, cooling the vagus nerves to a temperature sufficient to block the irritant reflex resulted in slow, deep breathing. At these temperatures, non-medullated fibres from J-receptors should still be conducting impulses. Further cooling did not change the respiratory pattern, confirming the studies of Guz and Trenchard (1971) which showed that the non-medullated fibres presumed to carry impulses from J-receptors are not involved in normal ventilatory control.

Although the Hering–Breuer inflation reflex was abolished and the high frequency bursts from slowly adapting receptors were probably blocked at the higher temperatures (Paintal 1966), there is still the possibility that the firing of some slowly adapting receptors is responsible for limiting tidal volume. For example, impulse volleys from slowly adapting receptors transmitted at different frequencies may have different central nervous system effects: the rapid bursts from low threshold slowly adapting receptors may delay the onset of the next inspiration, while slower firing volleys from high threshold receptors may serve to cut off inspiration. Another possibility is that the afferent signals are similar for the determination of the expiratory period and for termination of inspiration, but the central thresholds are different.

An alternate possibility is that stimulation of irritant receptors is responsible for terminating inspiration. In favour of this possibility is the fact that the cooling temperatures required to block the response to histamine aerosol (a substance known to stimulate irritant receptors) was similar to the temperature required to increase tidal volume. Irritant receptors do fire with rapidly adapting bursts at the end of inspiration (Mills et al. 1970, Sellick and Widdicombe 1971) but not usually with normal tidal volumes. However, it is likely that anaesthesia depresses irritant receptors. Furthermore, irritant receptor activity is increased markedly by the presence of smooth muscle tone in the airways where the receptors are presumably located (Mills et al. 1970). When neurophysiological studies of irritant receptor activity are performed, the vagus nerves are cut and the normal airway smooth muscle tone is abolished. In their description of irritant receptor activity, Sellick and Widdicombe (1971) suggested that irritant receptor discharge might be greater in the intact animal. Thus, the critical question remains whether irritant receptors normally fire during inspiration in the awake state. The

name "irritant" receptor suggests that their normal function is to respond to inhaled irritants. If they normally respond to lung stretch during inspiration and serve a function in the normal regulation of respiration, their name should be changed to one more appropriate to their function.

It is interesting that partial cooling of the vagus nerves resulted in an increase in the minute volume of ventilation and in a decrease in alveolar CO_2 tension, associated with a rapid, shallow breathing pattern. This pattern is reminiscent of the breathing that occurs when irritant receptors are stimulated by drugs or by inhaled irritants (Mills et al. 1970). Furthermore, the ventilatory response to inhaled CO_2 was actually increased when the vagi were partially cooled to temperatures at which the Hering–Breuer inflation reflex was abolished but the irritant reflex was enhanced. It is known that cooling the exposed vagus nerves to 7–12°C in dogs results in constriction of the airways, probably due to block of conduction in the afferent pulmonary stretch fibre pathway which has a tonic dilator influence on bronchial smooth muscle (Widdicombe and Nadel 1963). This tonic constriction increases the response of irritant receptors to lung inflation, and we suggest that this is the mechanism causing the decreased tidal volume, alveolar hyperventilation, and increased ventilatory responses to inhaled CO_2 and to inhaled histamine when the vagal loops were cooled from 16 to 9°C. This enhancement of response to inhaled CO_2 was abolished when the vagi were cooled further until the ventilatory response to inhaled histamine was abolished, suggesting that the slowly adapting receptors play an inhibitory role and the irritant receptors play an enhancing role on the ventilatory response to CO_2. The enhancing effect of vagal afferent activity has been confirmed in awake man, since the response to inhaled CO_2 is decreased when both cervical vagus nerves are blocked by local anaesthesia (Guz and Widdicombe 1969). The physiological response from slowly adapting receptors is weak in awake man in so far as the Hering–Breuer inflation reflex is concerned (Guz and Trenchard 1971), but responses to irritant receptor stimulation are potent (Widdicombe et al. 1962, Nadel et al. 1965). Therefore, it is likely that the enhancing effect of vagal afferent activity on the CO_2 response in man is due to stimulation of irritant receptors.

We suggest that the slowly adapting and irritant receptors may play opposing roles in the normal control of respiration in awake dogs. The reciprocal action of these two receptors is not unique to respiration, since they have opposing actions on bronchial smooth muscle: stimulation of the slowly adapting receptors inhibits vagal efferent activity in nerves innervating the airways and causes bronchodilation (Widdicombe and Nadel 1963), while stimulation of irritant receptors increases vagal efferent activity and causes bronchoconstriction (Sellick and Widdicombe

1971). Since the sensitivity of the irritant receptors is determined by the level of bronchomotor tone (Mills et al. 1970), the output from the slowly adapting and the irritant receptors may "set" the level of irritant receptor output and thereby serve as an autoregulatory system to adjust the pattern of breathing. It has been shown that there is an optimal frequency of breathing at which the work of breathing (Otis et al. 1950) and the mean force of respiratory muscle contraction (Mead 1960) are minimal, and that many mammals of different species breathe at a frequency close to optimal (Crosfill and Widdicombe 1961). This implies that a regulatory mechanism determines this optimum. We suggest that the interaction between slowly adapting and irritant receptors described above determine the appropriate respiratory pattern.

Reflex bronchoconstriction due to the inhalation of irritants in patients with airway obstruction (e.g., asthma) occurs at a lower threshold and is more severe than in healthy subjects (Simonsson et al. 1967), and we have suggested that this is due to "sensitization" of irritant receptors by the disease process. In addition, asthmatic patients usually manifest chronic alveolar hyperventilation unless airway obstruction is severe (McFadden and Lyons 1968), and we suggest that this may also be due to abnormal stimulation of irritant receptors. Inhaled irritants also cause a sensation of dyspnoea, and it is possible that stimulation of these receptors may be a cause of dysponea in patients with airway obstruction (Guz et al. 1970).

We have demonstrated that the respiratory response to the Hering–Breuer inflation reflex is abolished by unilateral vagotomy in awake dogs. Central multiplication of afferent stimuli has been demonstrated for other reflexes. If a similar process is present in vagal reflexes in man, this may account for the relief of dyspnoea that occasionally follows unilateral vagal blockade in patients with bilateral bronchopulmonary disease (Guz et al. 1970).

SUMMARY

1. The Hering–Breuer inflation reflex was present even in the normal tidal volume range in unanaesthetized dogs, but was weaker than during anaesthesia. Blockade of one vagus nerve abolished the Hering–Breuer inflation reflex in awake, but not in anaesthetized animals.

2. Bilateral complete vagal blockade in awake dogs resulted in slow, deep breathing, but there was no significant effect on arterial CO_2 tension or on apnoeic threshold CO_2 tension. This differs from results reported in anaesthetized dogs in which bilateral vagotomy produced a decrease in arterial CO_2 tension and in apnoeic threshold CO_2 tension.

3. In awake dogs, various stimuli, including auditory or visual distraction, increased body temperature, and exercise, decreased or abolished the Hering–Breuer inflation reflex, indicating that this vagal influence on respiration is modified markedly by stimulation of higher central nervous centres.

4. Bilateral complete vagal blockade decreased the response of minute volume of respiration (primarily by preventing an increase in respiratory frequency) during hypoxaemia and hypercapnia, but did not affect the response of respiratory frequency to increasing body temperature or to exercise. This suggests that the role of the vagi is to modulate respiratory input at the medullopontine level, but not in higher central nervous centres.

5. In awake dogs, progressive cooling of the exteriorized vagal loops from 16 to 9°C resulted in progressive abolition of the Hering–Breuer inflation reflex, but the respiratory response to inhaled histamine aerosol was not diminished or abolished. At these temperatures, the major alteration of respiratory pattern was a decrease in the expiratory phase of respiration. The tidal volume did not increase, but actually decreased. These findings suggest that the large fibres cooled at high temperatures and which are responsible for the Hering–Breuer inflation reflex determine the expiratory period of normal breathing. At these same temperatures, the dogs hyperventilated at rest and had an increased respiratory response to inhaled CO_2. We suggest that this could be due to stimulation of high threshold slowly adapting fibres but is more likely due to the effect of irritant receptors, which stimulate respiration but also may cut off inspiration prematurely (i.e., rapid, shallow breathing) when unopposed by bursts of slowly adapting receptor activity.

6. Further cooling of the vagal loops sufficient to abolish the respiratory response to inhaled histamine resulted in the slow, deep breathing pattern and impaired respiratory frequency response to inhaled CO_2 typical of the completely vagotomized animal.

7. We conclude that the slowly adapting and irritant receptors may have opposing actions which modulate the respiratory pattern. Effects of activity of these receptors on airway smooth muscle tone may serve an autoregulatory function in the normal control of respiratory rate and tidal volume.

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