J. Physiol. (1976), **258**, *pp.* 421–432
With 5 *text-figures*
Printed in Great Britain

TRANSDUCTION PROPERTIES OF TRACHEAL STRETCH RECEPTORS

BY D. BARTLETT, JR, G. SANT'AMBROGIO* AND J. C. M. WISE
From the Department of Physiology, St George's Hospital Medical School, London SW17 0QT

(*Received 17 November 1975*)

SUMMARY

1. Using single fibre vagal afferent recording, we have studied the behaviour of slowly adapting stretch receptors located in an isolated, *in situ*, segment of the trachea in dogs. Responses to positive and negative steady and oscillating transmural pressures were investigated.

2. Seventy-eight per cent of the receptors studied were tonically active at resting tracheal volume. Ninety per cent showed a more pronounced response to positive than to negative transmural pressures.

3. During pressure oscillations the majority of the receptors had a higher discharge frequency at any given pressure during the ascending phase of the pressure wave than at the same pressure under static conditions. During most of the ensuing descent of pressure toward zero the discharge frequency was lower than the corresponding static value. Thus discharge frequency led transmural pressure.

4. With increasing frequency of oscillation the differences from the static responses increased (dP/dt sensitivity), especially during the ascending limb of the pressure oscillation (rectifying behaviour).

5. In a small number of receptors, discharge frequency lagged behind transmural pressure or was in phase with it ('no loop' pattern).

6. In three cases the same receptor exhibited dP/dt sensitivity during positive pressure oscillations, whereas discharge frequency lagged behind pressure during negative pressure oscillations. This indicates that the lack of dP/dt sensitivity exhibited under negative pressure conditions does not represent an intrinsic property of these receptors, but reflects some aspect of their mechanical arrangement within the airway wall.

7. These patterns of response are discussed in terms of intrinsic and extrinsic characteristics of the receptors.

8. The physiological implications of stretch receptor behaviour are also considered.

* Reprint requests to: Dr G. Sant'Ambrogio, Department of Physiology, University of Texas Medical Branch, Galveston, Texas 77550, U.S.A.

INTRODUCTION

Mechanoreceptors placed in different structures have long been known to exhibit both static and dynamic properties, i.e. to respond both to maintained mechanical deformation and to its rate of change. Different types of receptors have different static and dynamic behaviour, and even within a single muscle spindle, endings specialized for either static or dynamic responses have been demonstrated (Cooper, 1961); furthermore, the same ending can be made to vary its transduction properties under different efferent influences (Matthews, 1962).

In some cases, the mechanical environment in which the receptor is suspended seems to play a prominent role in modifying its behaviour; this seems especially convincing in the case of the primary ending of the muscle spindle (Smith, 1966).

The static and dynamic behaviour of slowly adapting stretch receptors located along the airways has been studied by several investigators (Adrian, 1933; Knowlton & Larrabee, 1946; Widdicombe, 1954; Davis, Fowler & Lambert, 1956; Miserocchi & Sant'Ambrogio, 1974). This study is a further exploration of this problem.

We have studied the behaviour of receptors located in an isolated, *in situ* segment of the trachea, extending from the cricoid cartilage to the carina. Transmural pressure and volume of the segment could be varied independently from the rest of the bronchopulmonary structures. These two variables, pressure and volume, were therefore directly applicable to the segment in which the receptors were located, and the receptors could be studied without influence from respiratory movements.

The dynamic responses of airway stretch receptors have been previously described in terms of their responses to 'square wave' inflations through the evaluation of their 'adaptation index' (Knowlton & Larrabee, 1946; Widdicombe, 1954; Davis *et al.* 1956). This index has been variously defined but generally evaluates the amount of decay in the receptor's response after the maximum stimulus or the maximum activation of the receptor has been reached. The difficulty of introducing a true square wave stimulus to these airway receptors, especially when it is applied to the whole respiratory system, together with the necessarily inaccurate determination of the point of maximum stimulus, limits this analysis to an approximate estimate. We have therefore chosen to assess the dynamic behaviour of stretch receptors by determining their response to sinusoidally oscillating stimuli (Angell James, 1971).

METHODS

The studies were carried out in twenty-six dogs weighing 7–12 kg, anaesthetized by an intravenous injection of sodium pentobarbitone (30 mg/kg). Additional anaesthetic was given as needed. Plastic catheters were placed in a femoral artery and vein. Arterial blood pressure was monitored by means of a liquid-filled pressure transducer.

The trachea was cannulated just below the cricoid cartilage, and artificial ventilation was established by a Palmer pump. The chest was then opened on both sides between the fourth and fifth ribs. The entire left lung and the upper lobe of the right lung were removed, and the right mainstem bronchus was cannulated through the upper lobar bronchus. The connexion with the Palmer pump was then shifted from the tracheal to the bronchial cannula, and the dog was ventilated with 100% O_2 via the lower lobes of the right lung for the remainder of the experiment. A large surgical clamp was placed across the trachea just above its bifurcation, thus isolating the trachea from the remaining airways. The arrangement is described in greater detail elsewhere (Bartlett, Jeffery, Sant'Ambrogio & Wise, 1976).

Both vagosympathetic nerves were cut at the level of the cricoid cartilage. The peripheral cut end of the left vagus was placed in a dissecting tray through a lateral slit and covered with liquid paraffin. With the aid of a dissecting microscope, the fibrous and epineural sheaths were removed from the end of the nerve using iridectomy scissors and watchmaker's forceps. Small nerve filaments were placed on two platinum wire electrodes, and single unit afferent action potentials from slowly adapting stretch receptors were amplified, monitored by an oscilloscope and loudspeaker, and recorded on an ultraviolet recorder and on magnetic tape.

An instantaneous frequency meter, driven by the action potentials, was also used in some experiments. Its analogue output was registered on the ultraviolet recorder and on magnetic tape.

Positive or negative pressures could be applied to the tracheal segment, either as maintained, steady values or as approximately sinusoidal pressure oscillations produced by a motor-driven syringe pump. Transmural pressure in the segment was monitored by means of a pressure transducer connected to a side arm of the tracheal cannula. During sinusoidal oscillations the instantaneous position of the syringe pump piston was monitored by means of a linear potentiometer, the moving arm of which was mounted on the piston; the resulting crude volume signal was displayed on the ultraviolet recorder and on magnetic tape. Actual volume changes in the tracheal segment were calculated from the crude volume signal and the transmural pressure signal, taking gas compression or expansion into account.

Receptor identification and localization. Slowly adapting stretch receptors were considered to be located in the tracheal segment if their discharge frequency was influenced by changes in tracheal transmural pressure. All showed very slow adaptation at maintained pressures. Their location within the segment was determined by direct exploration through the tracheal cannula with a metal probe with a right angle bend 1 cm from its tip. By rotating the probe it was possible to determine the circumferential as well as the longitudinal position of the receptor in the tracheal segment (Bartlett *et al.* 1976).

Responses to maintained pressures. Steady pressures were applied to the segment through the tracheal cannula, and receptor discharge frequency was determined at least 5 sec after each pressure had been established; discharge frequency was essentially constant by this time. Positive and negative pressures between 0 and 30 cm H_2O were tested in steps of about 10 cm H_2O. Discharge frequency was plotted as a function of maintained transmural pressure for each receptor.

Responses to oscillating pressures. Sinusoidal volume oscillations resulting in transmural pressure swings between 0 and 25 cmH_2O (positive pressure oscillations) or between 0 and -25 to -40 cmH_2O (negative pressure oscillations) were applied to the tracheal segment at five different frequencies: 17, 38, 82, 176 and 220 cycles/min. Continuous records of discharge frequency, transmural pressure, and the crude volume signals were taken during several cycles at each frequency of oscillation. Loops of instantaneous discharge frequency plotted against transmural pressure were drawn by hand from the original record or displayed on a storage oscilloscope and photographed on Polaroid film.

A 'Dynamic Index' was derived to quantitate the difference between the static response of a receptor and the responses observed during pressure oscillations. The index was defined as the ratio of instantaneous discharge frequency at the mid-pressure point of the oscillation to the discharge frequency at the same pressure under static conditions. Thus Dynamic Index values great than 1 denote a discharge frequency greater than under static conditions; values less than 1 indicate a frequency below the static level. Dynamic index values were determined for both the ascending and descending parts of the pressure oscillations and for both positive and negative pressures.

RESULTS

Response to maintained pressures

We studied the responses of seventy-three slowly adapting stretch receptors to maintained pressures. Fifty-seven of these receptors (78 %) were active at the resting tracheal volume (zero transmural pressure). Sixty-six (90 %) showed a more pronounced response to positive than to negative pressures, five responded equally to positive and negative pressures, and two had a greater activation with negative pressures. When discharge frequency was plotted as a function of transmural pressure, we found a decreasing slope with increasing pressure in the case of sixty-five receptors (89 %). An example is shown in Fig. 1. These receptors would be characterized as Type I according to the classification of Miserocchi & Sant'Ambrogio (1974).

Responses to pressure oscillations

Forty-eight receptors were studied during the application of pressure oscillations to the tracheal segment. During the ascending phase of either positive or negative pressure waves, forty-four (92 %) had a discharge frequency, at any given pressure, higher than the corresponding static value. During most of the subsequent descending phase, in which transmural pressure returned toward zero, the discharge frequency was lower than under static conditions. Thus discharge frequency led transmural pressure throughout the oscillation (see Figs. 1 and 2). As illustrated in Fig. 1, at higher frequencies of oscillation, the differences from the static response increased, especially during the ascending limb of the positive or negative pressure wave. This phenomenon is also described in Fig. 3, which depicts the average ascending and descending Dynamic Index values for positive pressure oscillations at the various frequencies for all the receptors.

In contrast to the typical behaviour just described, two of the receptors had a lower than static discharge frequency during the ascending phase of

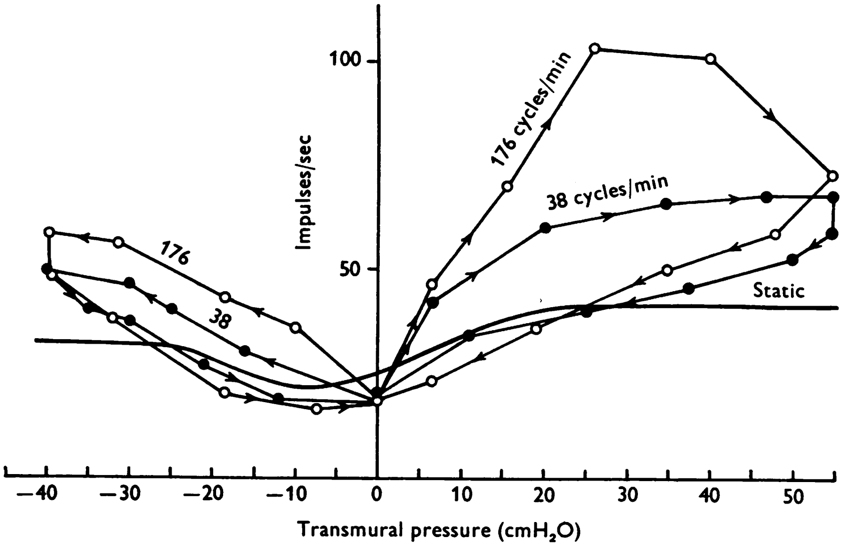

Fig. 1. Relationship between frequency of discharge (impulses/sec) of a tracheal stretch receptor and tracheal transmural pressure during 'static' (maintained pressures, heavy line) and dynamic conditions (oscillations at the two labelled frequencies). The loops (see arrows) indicate that the frequency of discharge leads transmural pressure.

Fig. 2. The record shows three cycles of the 'sinusoidal' oscillations of the tracheal segment in terms of: *A*, transmural pressure; and *B*, instantaneous frequency of discharge of a tracheal stretch receptor. Note that discharge frequency 'leads' transmural pressure.

the pressure oscillation (positive in one case and negative in the other), and a higher than static discharge frequency during the subsequent descending phase (Fig. 4). In the case of these receptors, discharge frequency lagged behind transmural pressure throughout the oscillation. At higher frequencies of oscillation this phase lag was increased, resulting in wider loops on the plot of discharge frequency *vs.* transmural pressure.

Two other receptors showed typical behaviour, with discharge frequency leading transmural pressure, during positive pressure oscillations, but showed no phase difference between discharge frequency and pressure during negative pressure oscillations, i.e. a 'no loop' pattern.

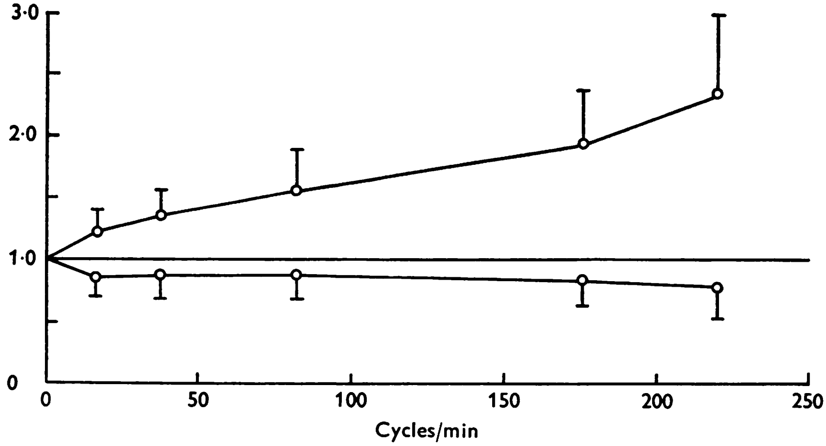

Fig. 3. Relationship between the 'Dynamic Index' (see text) and frequency of oscillations with positive pressure for the forty-four receptors in which discharge frequency led pressure. Values for the ascending phase are shown by the upper curve; those for the descending phase are shown by the lower curve. Vertical bars indicate 1 S.D. of observation.

Pressure–volume relations of the tracheal segment

Fig. 5 shows pressure–volume loops for a tracheal segment during the application of positive and negative pressures under quasistatic conditions ($\sim$ 3 cycles/min) and at two higher frequencies of oscillation. As expected, the segment exhibits some hysteresis, volume lagging slightly behind pressure in all trials. At higher frequencies of oscillation the loops show no tendency to widen, suggesting that the system has negligible resistive properties, even at 176 cycles/min. However the slope of the pressure–volume relationship decreased slightly as oscillation frequency increased, particularly at negative pressures. The origin of this effect is uncertain though the tendency for the pressure–volume loop to close at higher frequencies suggests a decreasing effective compliance due to failure of stress–relaxation to occur during the shorter available period.

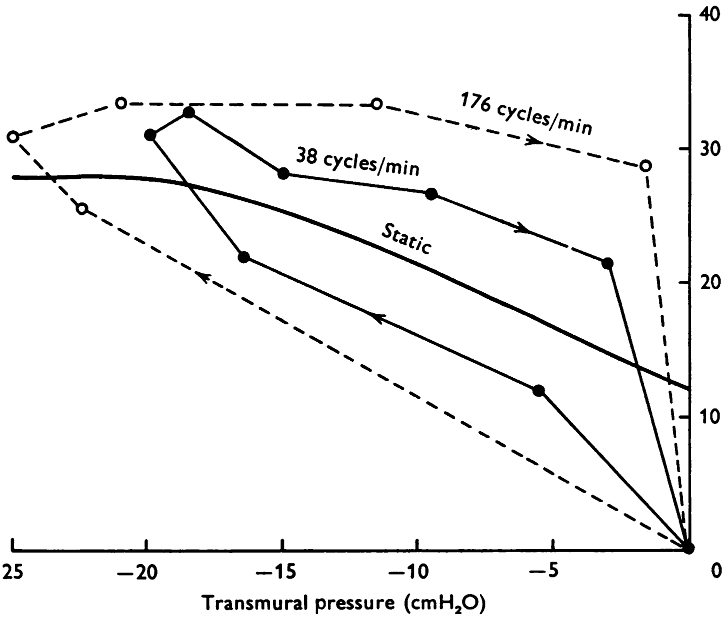

Fig. 4. Relationship between frequency of discharge (impulses/sec) of a tracheal stretch receptor and negative tracheal transmural pressure during 'static' (heavy line) and 'dynamic' conditions (oscillations at two different frequencies as indicated). In contrast with the receptor shown in Fig. 1 and Fig. 2 the discharge frequency lags behind the transmural pressure.

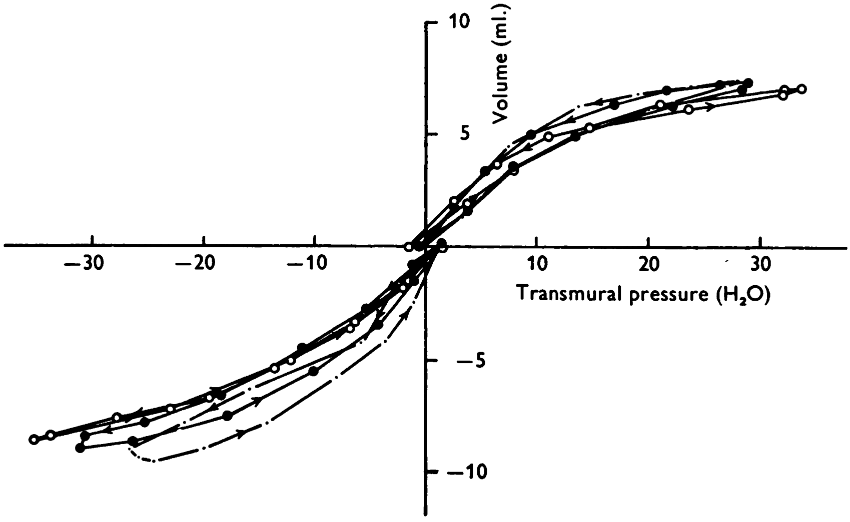

Fig. 5. Negative and positive transmural pressure–volume loops of the tracheal segment at three different frequencies of oscillations: —●—●—, quasistatic; —●—, 38 cycles/min; and —○—, 176 cycles/min.

DISCUSSION

Responses to maintained pressures

Most of the tracheal receptors studied were active at zero transmural pressure (resting tracheal volume). This finding is in agreement with the report of Miserocchi & Sant'Ambrogio (1974), who found tonic activity in a large proportion of stretch receptors located in extrapulmonary airways. As noted previously by several workers (Adrian, 1933); Paintal, 1966; Richardson, Sant'Ambrogio, Mortola & Bianconi, 1973), a considerable fraction of all 'pulmonary' stretch receptors exhibit tonic activity under experimental conditions. This fraction might be even greater under natural conditions, with normal airway innervation and smooth muscle tone, in view of the arrangement of the receptors in series with airway smooth muscle fibres (Widdicombe, 1954; Bartlett *et al.* 1976).

The majority of the tracheal receptors responded to both positive and negative pressures, as shown also by Widdicombe (1954). This behaviour is probably attributable to their location in the membranous posterior wall of the trachea, which is stretched by both positive and negative pressures (Bartlett *et al.* 1976). The fact that most of the receptors responded more to positive than to negative pressures (see also Widdicombe, 1954) suggests that they may be located in a part of the posterior wall with a smaller radius of curvature, and thus less circumferential tension, at a given negative pressure than at the corresponding positive pressure.

Responses to pressure oscillations

During positive pressure oscillations, even in quasistatic conditions, segment volume lags behind transmural pressure to some extent (Fig. 5): at any given pressure, volume is greater during the descending phase of the pressure oscillation than at the same pressure during the ascending phase. Since the distended trachea is essentially cylindrical, it follows that that radius of curvature of the airway wall is greater during the descending phase, and in accordance with the Laplace relationship, that circumferential tension at any given pressure is greater during the descending phase of the oscillation. Thus if a stretch receptor sensed only circumferential tension, its discharge frequency would lag behind transmural pressure, resulting in an anticlockwise loop on the diagram of discharge frequency plotted as a function of pressure.

During negative pressure oscillations the situation is more complicated. Volume still lags behind transmural pressure (Fig. 5), but since the evacuated tracheal segment with its inwardly bulging posterior wall is by no means cylindrical, no simple relationship between volume and radius of curvature exists. With increasing negative pressure, the radius of curvature at the posterior mid line and near the tips of the tracheal cartilages presumably becomes smaller, while the radius of curvature between the mid line and the lateral insertions of the muscle fibres must become greater. Because of these non-uniform changes in radius, the local circumferential tension and its direction of change with pressure changes must be quite different in different parts of the posterior tracheal wall. The discharge frequency of a stretch receptor sensing only circumferential tension would lag behind transmural pressure during negative pressure oscillations if it were located in a part of the wall that increases its radius of curvature as volume decreases. On the other hand, discharge frequency would lead transmural pressure if the receptor were located in a structure that decreases its radius as volume decreases.

In our experiments we found that during positive pressure oscillations, discharge frequency led transmural pressure in nearly all the receptors (Figs. 1 and 2). This behaviour indicates that the receptors are not simple tension sensors, but that their response has a dynamic component related to the rate of change of transmural pressure ($\mathrm{d}P/\mathrm{d}t$). The lack of $\mathrm{d}P/\mathrm{d}t$ sensitivity found in one of them might be attributed to a special location of the receptor, perhaps in that region of the smooth muscle overlying the end of the cartilage and therefore not necessarily to an intrinsic property of the receptor. No correlation was found between receptor's behaviour and its classification as Type I or Type II (Miserocchi & Sant'Ambrogio, 1974).

During negative pressure oscillations, receptor behaviour was much less uniform. In nine of twelve receptors studied, discharge frequency led transmural pressure, as in the case of positive pressure oscillations. In two receptors discharge frequency lagged behind pressure (Fig. 4), and in one receptor, discharge frequency and pressure were in phase during negative pressure oscillations (a 'no loop' pattern). This variety of receptor behaviour during oscillations with negative pressure probably reflects a balance between the intrinsic $\mathrm{d}P/\mathrm{d}t$ sensitivity of the receptors and the variety of factors influencing circumferential tension under negative pressure conditions, as discussed above.

In the case of three receptors, we observed typical behaviour, i.e. frequency leading pressure, during positive pressure oscillations, but the reverse pattern, with frequency lagging behind pressure, during negative pressure oscillations. This contrasting behaviour within individual receptors indicates that the lack of $\mathrm{d}P/\mathrm{d}t$ sensitivity exhibited under negative pressure conditions does not represent an intrinsic property of these receptors, but must reflect some aspect of their mechanical arrangement within the airway wall.

A purely static response (lack of dynamic response) in a receptor might reflect its arrangement 'in series' with a purely elastic element, whereas the presence of a purely dynamic response suggests an arrangement 'in series' with a purely viscous structure. A combination of these two situations would contribute to a combination of 'static' and 'dynamic' receptor properties (Matthews, 1962). In the case of tracheal stretch receptors we should consider not only the intrinsic visco-elastic properties of the smooth muscle fibres themselves, but also their coupling to the other structures that constitute the trachea. A separation between these factors, intrinsic and extrinsic to the smooth muscle, might be achieved by studying receptors' responses in isolated fragments of smooth muscles in which the force–length relationship is also studied.

A further interesting property exhibited by most of the receptors is shown in Fig. 1. During the ascending phase of pressure oscillations the discharge frequency exceeded the corresponding static value by an amount much greater than that by which the static discharge frequency exceeded the dynamically measured value during the descending phase. All the receptors were tested with oscillating pressures which exceeded their threshold of activation for most of the cycle: therefore it is apparent that the response to the positive rate of change in pressure is greater than the response to the negative rate of change in pressure. This behaviour could be described as a *true* rectifying property and it seems to differ from that found in the case of baroreceptors (Angell James, 1971). In the case of intrathoracic stretch receptors, this behaviour would enhance receptor discharge during inspiration ($\mathrm{d}P/\mathrm{d}t$ sensitivity), whereas during expiration discharge frequency would fall only slightly below the static curve. A further factor which increases this difference is that inspiratory flow is greater than expiratory flow in spontaneously breathing awake animals (Bendixen, Smith & Mead, 1964; Gautier, Remmers & Bartlett, 1973).

The dynamic behaviour of pulmonary stretch receptors has been studied previously by recording receptor discharge during 'square wave' inflations of the lungs and airways (Knowlton & Larrabee, 1946; Widdicombe, 1954; Davis *et al.* 1956). The $\mathrm{d}P/\mathrm{d}t$ sensitivity of most of the receptors, demonstrated by these earlier workers and in the present study, seems likely to play some role in the control of breathing. Clark & Euler (1972) found in anaesthetized cats that inspiration was terminated as effectively by gradual lung inflations as by rapid ones, suggesting that vagal feed-back is essentially determined by lung volume and is not influenced by its rate of change. However, recent experiments by Feldman & Gautier (1976) show a somewhat greater effectiveness of rapid inflations, as expected in view of the receptor properties. The reflex responses to lung inflation and deflation are not pure responses to changes in recruitment or discharge frequency of slowly adapting stretch receptors, but represent the net result of influences from these receptors and from other nerve endings, such as those serving irritant receptors (Mills, Sellick & Widdicombe, 1969; Sellick & Widdicombe, 1969). These different and sometimes conflicting influences presumably act together to modify the pattern of breathing.

We wish to thank Professor John G. Widdicombe for his interest in this investigation and for his hospitality in allowing us to use his laboratory.

This work was supported by a grant from the Medical Research Council. D.B. was the recipient of Public Health Research Career Development Award HL 70129 from the National Heart and Lung Institute, U.S.A. G.S. was the recipient of a grant from the Accademia Nazionale dei Lincei, Rome, in conjunction with the Royal Society.

REFERENCES

ADRIAN, E. D. (1933). Afferent impulses in the vagus and their effect on respiration. *J. Physiol.* **79**, 332–358.

ANGELL JAMES, J. E. (1971). The effects of altering mean pressure, pulse pressure and pulse frequency on the impulse activity in baroreceptor fibres from the aortic arch and right subclavian artery in the rabbit. *J. Physiol.* **214**, 65–88.

BARTLETT, D., JR, JEFFERY, P. K., SANT'AMBROGIO, G. & WISE, J. C. M. (1976). Location of stretch receptors in the trachea and bronchi of the dog. *J. Physiol.* **258**, 409–420.

BENDIXEN, H. H., SMITH, G. M. & MEAD, J. (1964). Pattern of ventilation in young adults. *J. appl. Physiol.* **19**, 195–198.

CLARK, F. J. & EULER, C. VON (1972). On the regulation of depth and rate of breathing. *J. Physiol.* **222**, 267–295.

COOPER, S. (1961). The response of the primary and secondary endings of muscle spindles with intact motor innervation during applied stretch. *Q. Jl exp. Physiol.* **46**, 389–398.

DAVIS, H. L., FOWLER, W. S. & LAMBERT, E. H. (1956). Effect of volume and rate of inflation and deflation on transpulmonary pressure and response of pulmonary stretch receptors. *Am. J. Physiol.* **187**, 558–566.

FELDMAN, J. L. & GAUTIER, H. (1976). The interaction of pulmonary afferents and pneumotoxic centre in control of respiratory pattern in cats. *J. Neurophysiol.* **39**, 31–44.

GAUTIER, H., REMMERS, J. E. & BARTLETT, D., JR (1973). Control of the duration of expiration. *Resp. Physiol.* **18**, 205–221.

KNOWLTON, G. C. & LARRABEE, M. G. (1946). A unitary analysis of pulmonary volume receptors. *Am. J. Physiol.* **147**, 100–114.

MATTHEWS, P. B. C. (1962). The differentiation of two types of fusimotor fibre by their effects on the dynamic response of muscle spindle primary ending. *Q. Jl exp. Physiol.* **47**, 326–333.

MILLS, J. E., SELLICK, H. & WIDDICOMBE, J. G. (1969). Activity of lung irritant receptors in pulmonary microembolism, anaphylaxis and drug-involved broncho-constrictions. *J. Physiol.* **203**, 337–357.

MISEROCCHI, G. & SANT'AMBROGIO, G. (1974). Responses of pulmonary stretch receptors to static pressure inflations. *Resp. Physiol.* **21**, 77–85.

PAINTAL, A. S. (1966). Re-evaluation of respiratory reflexes. *Q. Jl exp. Physiol.* **51**, 151–163.

RICHARDSON, P. S., SANT'AMBROGIO, G., MORTOLA, J. & BIANCONI, R. (1973). The activity of lung afferent nerves during tracheal occlusion. *Resp. Physiol.* **18**, 273–283.

SELLICK, H. & WIDDICOMBE, J. G. (1969). The activity of lung irritant receptors during pneumothorax, hyperpnoea and pulmonary vascular congestion. *J. Physiol.* **203**, 359–381.

SMITH, R. S. (1966). Properties of intrafusal muscle fibres. In *Muscular Afferents and Motor Control*, ed. GRANIT, R., pp. 69–80. Stockholm: Almqvist and Wiksell.

WIDDICOMBE, J. G. (1954). Receptors in the trachea and bronchi of the cat. *J. Physiol.* **123**, 71–104.