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LOCALIZATION OF PULMONARY STRETCH RECEPTORS IN THE AIRWAYS OF THE DOG

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SUMMARY

1. During respiratory efforts against a closed airway, the afferent activity of vagal fibres from pulmonary stretch receptors does not appreciably increase during the inspiratory phase because the lung is prevented from expanding.

2. Occlusion at different levels of the airways allows the localization of pulmonary stretch receptors in the tracheo-bronchial tree.

3. 144 fibres from pulmonary stretch receptors on the left side of the tracheo-bronchial tree have been studied in eleven dogs and their localization was as follows: 17·4 % in the upper half of the intrathoracic trachea, 27·1 % in the lower half of the intrathoracic trachea and the carina, 11·1 % in the main bronchus, 13·9 % in the upper lobe and 30·5 % in the lower lobe.

4. From the surface area of the tracheo-bronchial tree at different levels on the assumption of a total of 2000 stretch receptors on each side, their average concentration was as follows: 34·8 % receptors/cm^2 in the upper half of the intrathoracic trachea, 54·2/cm^2 in the lower half of the intrathoracic trachea, 56·8/cm^2 in the main bronchus, 0·37/cm^2 in the intrapulmonary airways.

5. Occlusion of the main bronchus caused an increase of the eupnoeic oesophageal pressure swing by about 75 % whereas occlusion of the inferior lobar bronchus led to an increase of only 20 %. Therefore the reflex effects induced on the respiratory activity by occluding the airways at various levels show the greatest importance of the hilar portions of the airways where the concentration of pulmonary stretch receptors has been found to be greater.

INTRODUCTION

Pulmonary stretch receptors are usually identified with the smooth muscle ending which occur throughout the tracheo-bronchial tree (Widdicombe, 1964). Their precise localization along the airways is still mostly

unknown; Elftman (1943) reported, on histological basis, that they become less frequent in the narrower airways, and Richardson, Sant'Ambrogio, Mortola & Bianconi (1973), probing the lungs in open-chested rabbits, found that 63% (twelve out of nineteen fibres) of pulmonary stretch receptors were localized within 1 cm from the lung's root.

It has been shown that during a respiratory effort against closed airways the afferent activity of vagal fibres from pulmonary stretch receptors does not increase appreciably during the inspiratory phase because the lung is prevented from expanding (Weidman & Bucher, 1951; Widdicombe, 1961; Richardson *et al.* 1973). This observation together with the possibility of performing occlusion at different levels along the tracheo-bronchial tree down to the lobar bronchi allows the localization of pulmonary stretch receptors in the airways.

METHODS

Experiments were performed on eleven dogs (weight range 10–30 kg) anaesthetized with an I.V. injection of a mixture of urethane and chloralose (initial dose 4 ml./kg body wt. of a solution of urethane 25% and chloralose 2·5%). At the beginning of the experiment we injected I.V. a clotting substance (emocoagulase) which proved to be very useful to reduce bleeding while the vagus nerve was dissected.

A cannula having a lateral branch at a 35° angle was inserted into the lower part of the extrathoracic trachea and the left vagus nerve was exposed in the neck and dissected from the surrounding tissues down to its entrance into the thorax. The afferent supply from the extrathoracic trachea through the recurrent laryngeal nerve was damaged and could not be considered in this study. The vagus was then cut at the level of the second tracheal ring and a length of about 2 cm of its peripheral cut end was placed through a lateral slit on a dissecting tray which was flooded with paraffin oil. Isolation and subsequent microdissection of the vagal fibres were carried out under oil with the aid of a binocular microscope using a pair of iridectomy scissors and watchmaker forceps to remove the fibrous and the epineural sheets and to tease from the whole nerve small filaments containing a few or one active fibres. These small filaments were then placed on two platinum electrodes connected to a conventional a.c. amplifier (Tektronix RM 122) whose signals were then fed into a 565 Tektronix oscilloscope and to a loudspeaker amplifier. Intrathoracic pressure was recorded through an oesophageal latex balloon connected to a Statham pressure transducer. On some occasions intratracheal pressure was recorded through a side opening of the tracheal cannula connected to a Statham transducer, and tidal volume from a pneumotachograph and a Godart volume integrator.

Bronchial catheterization. The distance of the tracheal bifurcation (carina) from the entrance of the tracheal cannula was assessed using a device described by Miserocchi, D'Angelo, Michelini & Agostoni (1972). It consists of a metal tube having at one end two aluminium plates mounted on a pivot. A metal wire running into the tube was connected to each plate; by pulling the wire the plates could pivot in opposite directions. The tube, with the plates superimposed was inserted into the trachea through the straight branch of the tracheal cannula and pushed down to the carina; then, by pulling the wire, the plates were wedged in the two main bronchi. The distance from the carina to the branching of the main bronchus in the two lobar bronchi was previously established in a few dead open-chested dogs (10–30 kg).

Selective occlusion at different levels of the tracheo-bronchial tree was performed using a rubber tube for endobronchial intubation (Rüsch no. 12) having an inflatable cuff around its tip. Catheterization of the lobar bronchi was obtained with the aid of specially shaped steel mandrils inserted through the rubber tube. Proper catheterization using these mandrils had been previously checked in open-chested dogs.

Type of receptors. The receptors we considered were those which showed progressively increasing rates of discharge during the inspiratory phase of an eupnoeic breath; those which showed an activity at FRC level had their discharge reduced and eventually stopped by a lung deflation to -5 or -10 cm H_2O. They all showed a very slow adaptation at maintained positive pressure. We used the expression 'pulmonary stretch receptors' as a generic term which applies also to the endings localized in the extrapulmonary airways.

Localization of the receptors. Occlusion either of the superior or of the inferior lobar bronchus led to the localization of pulmonary stretch receptors in either one of these lobes. A pulmonary stretch receptor whose activity was still modulated during the respiratory effort after the occlusion of the lobar bronchi should be localized above in the tracheobronchial tree; thus further occlusions at higher levels allowed its localization in the main bronchus or in the trachea. Direct stimulation of stretch receptors, localized in the main bronchus or in the trachea, was also sometimes possible when the cuff of the catheter was inflated. These procedures have been applied only to the left side of the intrathoracic tracheo-bronchial tree.

Analysis of fibre behaviour. For each stretch fibre studied we plotted a frequency histogram of its activity through the respiratory cycle both in the control breath and with tracheal occlusion. From this we have compared the modulation of the discharge during airway occlusion with the modulation in the control breath. We have done this by measuring the difference in the mean frequency of firing between inspiration and expiration of the respiratory effort. This is then expressed as a function of the same difference in the control breath. This is defined as the modulation index (Richardson *et al.* 1973). A fibre which fires more during the inspiratory phase of the tracheal occlusion has a positive modulation index, whereas a fibre firing more during the expiratory phase would have a negative modulation index.

Reflex effects of occlusion of the airways at different levels. In four additional dogs with the same anaesthesia and prepared in the same manner with the exception that both the vagus nerves were intact we measured oesophageal pressure during control eupnoeic breathing and after occlusion of either the main bronchus or the lobar ones. This allows the study of the reflex effects of the sudden withdrawal of different amounts of afferent activity coming from the pulmonary stretch receptors localized below the point of occlusion.

RESULTS

Localization of pulmonary stretch receptors. Fig. 1 illustrates the behaviour of a pulmonary stretch receptor localized in the lower trachea, showing that its response to inspiration is present during occlusion of the left main bronchus, and is abolished by occlusion of the trachea 2–3 cm above the carina.

Fig. 2 illustrates the behaviour of a pulmonary stretch receptor localized in the left upper lobe, showing that its response to inspiration is present on occlusion of the lower bronchus, but is abolished on occlusion of the left main bronchus, the upper lobar bronchus, or the intrathoracic trachea.

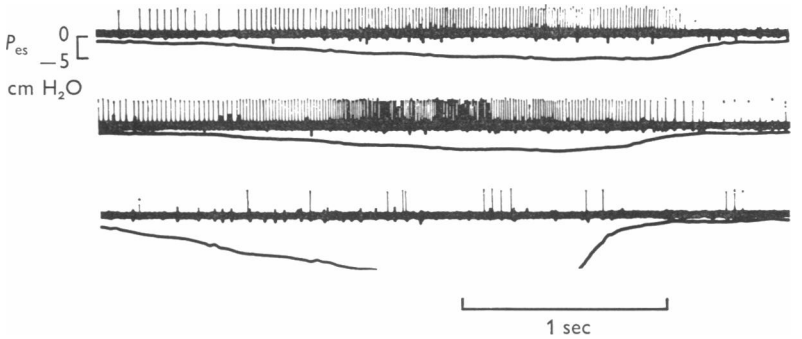

Fig. 1. Anaesthetized dog. Action potentials from a vagal single fibre coming from a pulmonary stretch receptor (top tracing in each record) and intra-oesophageal pressure (lower tracing in each record). Top record: control breath, middle record: occlusion of the left main bronchus, lower record: occlusion of the trachea 2–3 cm above the carina. This stretch receptor was localized at the carina. In the middle record the increased activity observed throughout the respiratory cycle might be due to the direct stimulation by the inflated cuff placed just below the receptor.

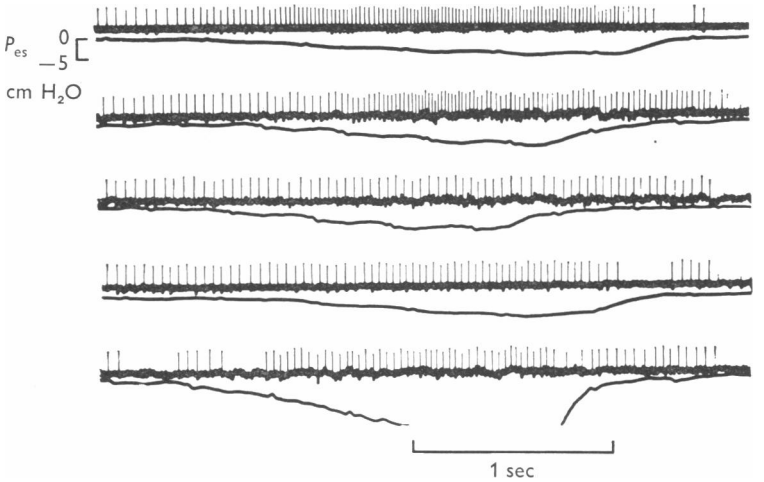

Fig. 2. Anaesthetized dog. Action potentials from a vagal single fibre coming from a pulmonary stretch receptor (top tracing in each record) and intra-oesophageal pressure (lower tracing in each record). From top to bottom: control breath, occlusion of the lower lobar bronchus, occlusion of the left main bronchus, occlusion of the upper lobar bronchus, occlusion of the intrathoracic trachea. This stretch receptor was localized in the left upper lobe.

Table 1 summarizes the results obtained from 144 fibres from eleven dogs. It appears that 55·6 % of the fibres come from pulmonary stretch receptors localized in the larger airways down to the main bronchus, whereas 44·4 % come from the intrapulmonary airways.

TABLE 1. Localization of 144 stretch receptors (PSR) in the tracheo-bronchial tree of eleven dogs

	Extrapulmonary airways			Intrapulmonary airways	
	Main bronchus	Lower half intrathoracic trachea	Upper half intrathoracic trachea	Lower lobe	Upper lobe
No. of receptors	16	39	25	44	20
%	11·1	27·1	17·4	30·5	13·9
PSR/cm²	56·8	54·2	34·8	0·37	

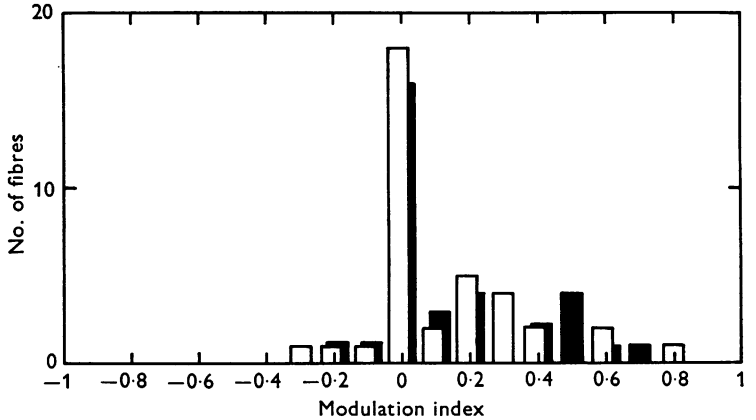

Fig. 3. Frequency histograms for the modulation index calculated from seventy-two fibres coming from stretch receptors localized either in the extrapulmonary (open column) and intrapulmonary (filled column) airways.

The modulation index was calculated for seventy-two fibres coming either from extra- or intra-pulmonary airways. Fig. 3 shows the frequency distribution of the modulation index for fibres coming from extrapulmonary (white columns) and intrapulmonary airways (stippled columns). No significant difference exists between the modulation index of the two groups (0·16 ± 0·03 (S.E.) for the extrapulmonary and 0·14 ± 0·04 for the intrapulmonary) and the average modulation index for all the fibres is 0·15 ± 0·02 (S.E.).

Reflex effects. The increases of oesophageal pressure swing (means and standard errors) occurring during the first breath after occlusion of the

main bronchus, of the lobar inferior bronchus and of the lobar superior bronchus were respectively: $76{\cdot}2 \pm 10{\cdot}9$, $23{\cdot}3 \pm 1{\cdot}8$ and $7{\cdot}3 \pm 1{\cdot}5\%$. After vagotomy the changes of intraoesophageal pressure with occlusion of either the main bronchus or the lobar bronchi are markedly less pronounced (see Figs. 1 and 2).

DISCUSSION

From the data of Table 1 (2nd row) and from the surface area of the various portions of the tracheo-bronchial tree, it is possible to calculate the average concentrations of pulmonary stretch receptors per unit surface area in the various regions (Table 1, 3rd row), knowing the total number of pulmonary stretch receptors on each side. 1200 myelinated afferent fibres have been described in the cat as coming from the bronchi (Agostoni, Chinnock, Daly & Murray, 1957); since we have considered also the stretch fibres originating in the intrathoracic trachea which account for 45·3% (see Table 1) of the receptors localized (about 1000) the total number of myelinated fibres coming from stretch receptors would be about 2000 considering that about 10% of the myelinated fibres come from irritant receptors (Widdicombe, 1954). The mean surface area of one half of the intrathoracic trachea in our dogs was about 20 cm^2. Thus the concentration of pulmonary stretch receptors in the higher half of the intrathoracic trachea would be $17{\cdot}4/100 \times 2000/10 = 34{\cdot}8/cm^2$. The same calculation leads to a concentration of $54{\cdot}2/cm^2$ in the lower half of the intrathoracic trachea. The mean surface area of a main bronchus was 3·9 cm^2 giving a concentration of 56·8 pulmonary stretch receptors per cm^2. We assume that the numbers of fibres in the cat are also applicable to the dog; even if this assumption is quantitatively inaccurate it will make no difference to the relative concentrations of receptors.

Slowly adapting receptors were localized in the trachea and in the main bronchus of the cat by direct stimulation through a catheter (Widdicombe, 1954). There seems to be a good agreement with these data which also showed an increasing concentration of slowly adapting receptors from the higher intrathoracic trachea to the main bronchus.

While all the receptors in the main bronchus were localized by direct stimulation through the inflated cuff, this was possible only in about 10% of the receptors localized in the intrathoracic trachea. Elftman (1943) described perichondral receptors morphologically similar to those found in the smooth muscles of the tracheo-bronchial tree. If they had the physiological behaviour of stretch receptors this might account for the difficulty found in stimulating them directly through the cuffed catheter. These receptors were also seen in the main bronchus (Elftman, 1943) but because

of the greater compliance of this structure they might be more easily stimulated.

From the morphometric data of Weibel in man (1964) the surface area of the intrathoracic trachea plus that of the main bronchus is about 100 times less than that of the intrapulmonary airways (including bronchioles and alveolar ducts). If the same proportion exists in the dog the mean concentration of pulmonary stretch receptors in the intrapulmonary airways would be about 0·37/cm^2. As shown in Table 1 the number of pulmonary stretch receptors in the inferior lobe is 2·2 times greater than in the superior lobe. Since about the same ratio exists between the volumes of the two lobes the stretch receptor concentrations in them should not differ markedly. It appears that the concentration of pulmonary stretch receptors per unit surface area increases by about 1·5 times going from the upper intrathoracic trachea to the main bronchus and then decreases by about 150 times in the intrapulmonary airways. We have no information on the distribution of pulmonary stretch receptors throughout the lung parenchyma.

The modulation index does not differ between the extrapulmonary and the intrapulmonary stretch receptors. It is however greater than that found in rabbits and cats (Richardson *et al.* 1973). This could be due to a different behaviour of pulmonary stretch receptors or to a different degree of deformation undergone during an inspiratory effort by the occluded regions of the lung. The second hypothesis seems however less probable since the relative decrease of the lateral diameter of the rib cage during an occluded breath, and the alveolar pressure developed, are essentially similar in rabbits, cats and dogs (E. D'Angelo & G. Sant'Ambrogio, unpublished).

The modulation index of pulmonary stretch receptors localized in a lobe is essentially equal whether the occlusion is performed at the level of the lobar bronchus or above. This fact is perhaps surprising since D'Angelo, Miserocchi, Michelini & Agostoni (1973) found that the inferior lobe undergoes a different deformation when occlusion is performed at the level of the lobar or of the main bronchus.

The reflex effects on respiratory activity induced by occluding the airways at various levels show the greatest importance of the hilar portion of the airways. Indeed it is quite apparent that the changes induced in the oesophageal pressure swings are far greater when occlusion is performed at the level of the main bronchus than at the level of the lobar bronchi. Therefore the inspiratory effort is far greater when also the main bronchus and its bifurcation into the lobar bronchi, despite the small surface area, are prevented from expanding; this fact is in good agreement with the data discussed above which indicate a greater concentration of pulmonary stretch receptors in this region. The inflated cuff should stimulate the

stretch receptors placed in the walls of the airway in contact with it and thus cause some inhibition of the inspiratory output. In few occasions, during occlusion of the main bronchus, we observed a lengthening of the expiratory pause, in addition to the increase in inspiratory effort. This fact may suggest that the most of the stretch receptors are localized at the points of branching of the main bronchus into the lobar bronchi where they cannot be easily reached by the inflated cuff. This consideration is substantiated by the data reported by Elftman (1943) and Widdicombe (1954) showing a greater concentration of pulmonary stretch receptors at the points of branching of the tracheo-bronchial tree.

If pulmonary stretch receptors are concerned with the regulation of depth and rate of breathing one may speculate that the greater concentration of these receptors in the larger airways could be related to the fact that the transmural pressure across these airways is less affected by local differences of transmural pressure at lobar levels (atelectasis, fibrosis) and thus they could better detect the average transmural pressure normally acting on the lung during the respiratory cycle.

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