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Lung mechanics and activity of slowly adapting airway stretch receptors

F.B. Sant'Ambrogio, G. Sant'Ambrogio, J.T. Fisher

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ABSTRACT: Transpulmonary pressure is thought to be closely associated with slowly adapting mechanoreceptor activity. The transpulmonary pressure required to inflate the lung to a given volume depends on pulmonary compliance: for equal tidal volumes less pressure will be required if compliance is higher. Therefore, an inverse relationship is expected between receptor activity and lung compliance for equal changes in lung volume. We have studied 33 slowly adapting airway stretch receptors (SARs) in anaesthetized, vagotomized, paralysed and artificially ventilated dogs, with the chest open, at constant tidal volume and frequency. After lung compliance had been increased by hyperinflation, all of the ten tracheal receptors studied and fourteen of the 23 intrapulmonary receptors reduced their activity. Of the remaining intrapulmonary receptors five increased their activity and four were unaffected. Our results indicate that, although airway stretch receptor discharge is usually related to transpulmonary pressure, this relationship is not always present in the case of peripherally located endings; this is possibly due to a discrepancy between local transmural pressure and overall transpulmonary pressure. Thus, in addition to the well described independence of SAR discharge frequency from lung volume, the activity of SARs having peripheral locations is not always predictable on the basis of changes in transpulmonary pressure.

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Department of Physiology and Biophysics, University of Texas Medical Branch, Galveston, Texas 77550 and Department of Physiology, Queen's University, Kingston, Ontario.

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In 1933, ADRIAN [1] postulated that the activity of slowly adapting pulmonary mechanoreceptors was related to lung volume. Later, KNOWLTON and LARRABEE [2] demonstrated that lung volume could not be directly responsible for the activation of these endings, since a constant volume inflation was seen to be less effective when lung compliance was increased. These results indicated that transpulmonary pressure was more directly responsible than lung volume for stimulating stretch receptors. Later studies by WIDDICOMBE [3] and DAVIS *et al.* [4] confirmed this hypothesis.

The aim of this study is to re-examine the relationship between transpulmonary pressure (and lung compliance) and airway stretch receptor activity, and to determine whether the location of receptors within the tracheobronchial tree plays a role in their response. Since measurement of pressure oscillations during the breathing cycle at the airway opening is not representative of the pressure exerted on the walls of bronchi and bronchioles and since the most peripheral airways are more susceptible to collapse [5], we postulated that there might be divergent behaviour between transpulmonary pressure (measured at the airway opening) and stretch receptor discharge for nerve endings localized in distal airways.

Methods

Experiments were performed on eight mongrel dogs of either sex, (weight range: 12–15 kg), anaesthetized intravenously with a mixture of alpha-chloralose (0.1 $g \cdot kg^{-1}$) and urethane (1.0 $g \cdot kg^{-1}$). The animals were placed in a supine position on an operating table and a polyethylene catheter was inserted in a femoral vein for administration of additional doses of anaesthetics as needed or injection of other drugs; a second polyethylene catheter was placed in a femoral artery and connected to a pressure transducer to monitor arterial blood pressure. An incision was made in the neck and a Y-shaped cannula inserted in the trachea just below the cricoid cartilage. One arm of the tracheal cannula was connected to a Statham pressure transducer to measure tracheal pressure and the other arm to a Fleisch pneumotachograph with a differential pressure transducer for measuring respiratory airflow and volume. The dogs were then paralysed with gallamine (4 $mg \cdot kg^{-1}$) and artificially ventilated with a Harvard constant volume pump at a frequency and a tidal volume adequate to maintain end-tidal carbon dioxide pressure (P_{CO_2}) between 4.5 and 5.3 kPa (35–40 mmHg). The sternum was split along its

midline and the chest kept widely open with a rib-spreader so that tracheal pressure reflected transpulmonary pressure (Ptp). An end-expiratory pressure of 0.3–0.4 kPa was maintained by immersing the outlet of the respirator in water.

Both vagus nerves were cut high in the neck; the peripheral cut end of the right vagus was freed from the surrounding tissues for a length of 3–4 cm, placed on a dissecting tray filled with paraffin oil and desheathed. Thin filaments were separated from the main trunk of the nerve using watch-maker forceps, with the aid of a binocular dissecting microscope. Each filament was placed on a pair of platinum electrodes connected to an AC-coupled amplifier and the action potentials were displayed on an oscilloscope in parallel with a loudspeaker. Dissection of each filament was continued until a single unit was found. A slowly adapting mechanoreceptor was identified by its regularly increasing discharge with each breath and slow adaptation to a maintained pressure.

The amplified signal of receptor discharge was fed into a window discriminator/rate meter and the discharge frequency, tidal volume and tracheal pressure were displayed on a pen recorder (Gould-Brush 2400).

The hyperinflation always caused an increase in lung compliance as indicated by a lower peak transpulmonary pressure. Several trials were performed for each receptor at intervals of 5–10 min to allow a return of lung compliance to its control value.

At the completion of the protocol the location of each receptor was ascertained. A Foley catheter was placed in the trachea, as caudally as possible, the cuff was then inflated and the catheter withdrawn; this procedure would stimulate a receptor located in the trachea. If the result was negative the lung was gently manipulated to stimulate the receptor and localize it within a lobe. For two receptors a more accurate localization was performed by dissecting the lung parenchyma starting from the periphery, after having ligated the corresponding lobar artery. The lumen of each exposed cut bronchus was probed with a thin nylon thread or small catheter to stimulate the receptor and the diameter of the bronchus in which it was localized was measured.

The average peak Ptp, peak frequency of receptor discharge and number of action potentials per respiratory cycle for three breaths immediately preceding hyperinflation were considered as control values.

Table 1. – Changes in transpulmonary pressure and slowly adapting stretch receptor activity

	post-inflation breath	Ptp % of control	Impulse frequency imps·s^{-1} at peak % of control	Impulse frequency imps·s^{-1} at FRC % of control	No. of impulses % of control T_I	No. of impulses % of control T_E
a)	I	73.5±3.4	75.0±3.6 (10)	62.71 (5)	55.9±4.1 (2)	- (0)
	II	72.7±3.4	76.4±4.3 (10)	64.30 (5)	85.0±8.2 (2)	- (0)
	III	70.6±3.4	75.3±4.1 (9)	87.50 (5)	75.0 (1)	- (0)
b)	I	76.5±2.6	58.3±6.8 (14)	105.0 (1)	34.4±5.9 (8)	- (0)
	II	74.9±2.7	66.0±7.1 (14)	105.0 (1)	35.3±7.5 (8)	- (0)
	III	75.2±2.6	71.6±7.4 (14)	105.0 (1)	60.1±10.9 (8)	- (0)
c)	I	88.2±0.5	94.0±1.6 (4)	71.0 (1)	81.3 (2)	75.0 (1)
	II	89.2±1.8	94.0±2.0 (4)	75.0 (1)	87.5 (2)	75.0 (1)
	III	89.2±1.8	95.1±1.8 (4)	100.0 (1)	92.6 (2)	98.0 (1)
d)	I	73.4±2.8	146.6±19.2 (5)	53.1 (2)	225.5 (1)	6.3 (1)
	II	70.5±2.8	150.5±23.1 (5)	71.6 (2)	259.4 (1)	61.7 (1)
	III	71.8±2.4	141.1±15.6 (5)	98.7 (2)	177.9 (1)	62.2 (1)

Average data (±SE) are grouped according to location of receptors and their responses in the first (I), second (II) and third (III) breath after hyperinflation. a: extrapulmonary SAR; b: intrapulmonary SAR with decreased activity; c: intrapulmonary SAR with no change in activity; d: intrapulmonary SAR with increase in peak activity; T_I: inspiratory time; T_E: expiratory time; FRC: functional residual capacity. Numbers in parentheses respresents number of receptors.

For each receptor the following protocol was used: control breaths were recorded; the outlet of the respirator was occluded for the duration of 3–4 pump cycles to hyperinflate the lungs (Ptp=2.5–3.0 kPa); the occlusion was removed and the lungs were allowed to reach their previous end-expiratory pressure; meanwhile the mechanical ventilation continued at a constant tidal volume. The corresponding values of the first, second and third breath following hyperinflation were expressed as percentages of control values. A receptor was defined as being affected by the challenge when its rate of discharge was changed by 10% or more during the first and second post-inflation pump cycle. Results are given as mean values±standard error (SE)

Results and discussion

Without exception, peak transpulmonary pressure decreased after lung hyperinflation (breath I: 76.6±1.8%; breath II: 75.3±1.9%; breath III: 75.2±1.9% of control values) indicating an increase in dynamic compliance (from 0.19±0.01 $l \cdot kPa^{-1}$ to 0.27±0.02 $l \cdot kPa^{-1}$ for the first breath). These values of dynamic compliance are similar to those reported by JONZON *et al.* [6], for artifically ventilated open chest dogs, and at the lower end of the range found by CROSFILL and WIDDICOMBE [7] in spontaneously breathing dogs.

Thirty-three receptors were studied. The ten SARs that were located in the trachea and extrapulmonary bronchi decreased their peak rate of discharge after lung hyperinflation (table 1). In addition, fourteen of the 23 intrapulmonary receptors studied behaved in a similar manner (fig. 1); one of them was localized in a bronchus of 5 mm diameter. Of the remaining nine intrapulmonary receptors, four maintained the same peak rate of discharge after hyperinflation (one was localized in a bronchus of 1.2 mm diameter) and five increased their rate of discharge (fig. 2). Although the precise location of eight of these nine receptors could not be established, manipulation of the lobe suggested a highly peripheral location within the lung.

Activity at functional residual capacity (FRC) was present in five of the ten extrapulmonary receptors and, after lung hyperinflation, decreased in a similar way to the inspiratory activity (table 1). For each group only a few intrapulmonary receptors were active at FRC (table 1). A steady state transpulmonary pressure and rate of receptor discharge was reached after 4–6 breaths.

The observation that transpulmonary pressure, rather than lung volume, is a more representative stimulus for activating SARs was clearly demonstrated by KNOWLTON and LARRABEE [2], (see their fig. 16), and later confirmed by WIDDICOMBE [3] and DAVIS *et al.* [4]. However, transmural pressure does not always have the attributes of a "proper" stimulus for the activation of airway SARs. In fact, in special circumstances, SAR activity can vary in an opposite direction to transmural pressure and the magnitude of its change cannot always be accounted for by the concurrent changes in transmural pressure [8]. Indeed, the tension developed by trachealis muscle contraction is related to tracheal SAR discharge, whilst changes in transmural pressure are not necessarily representative of SAR activation.

The present results seem to provide another example of possible dissociation between transpulmonary pressure and receptor activity for a minority of SARs localized in the lung periphery. However, in this case the

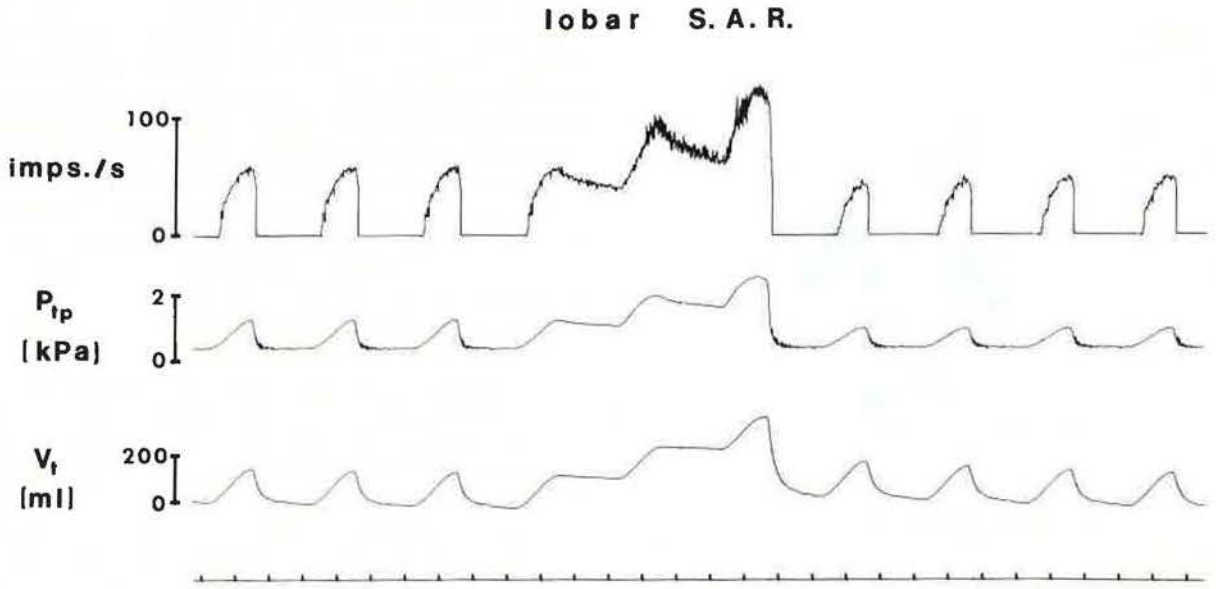

Fig. 1. – Activity of receptor localized in the lower lobe of the right lung. From top to bottom: imps·s^{-1}: rate of discharge of the receptor; Ptp: transpulmonary pressure; VT: tidal volume; time in s. Note that after hyperinflation tidal volume was the same as during control, but peak transpulmonary pressure was lower; this was accompanied by a decrease in peak receptor activity.

Whilst all tracheal and extrapulmonary bronchial SARs showed a decrease in their peak inspiratory activity following lung hyperinflation, concurrent with the decrease in peak transpulmonary pressure (table 1), there were notable exceptions among those SARs localized within the lungs (table 1 and fig. 3). The number of action potentials per cycle computed for thirteen SARs changed after lung hyperinflation in a parallel manner with the peak rate of discharge (table 1).

divergent relationship between transpulmonary pressure (decreasing after lung hyperinflation) and SAR discharge (increasing after lung hyperinflation) could be interpreted as depending on the location of the particular receptor in a region of atelectasis not in communication with the central airways. It is only with hyperinflation that this region would become fully ventilated and SARs exposed to the transpulmonary pressure responsible for the mechanical events. Only under these circumstances would

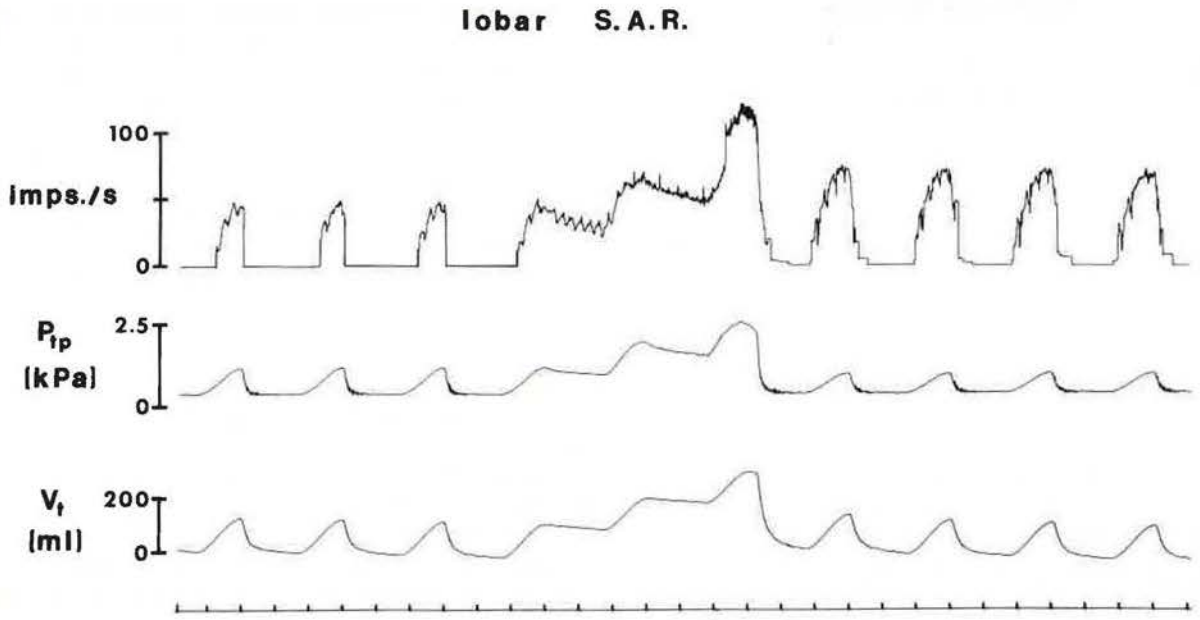

Fig. 2. – Activity of receptor localized in the middle lobe of the right lung. Symbols as in fig 1. The peak activity of this receptor increased following the hyperinflation of the lungs in spite of a decrease in peak transpulmonary pressure.

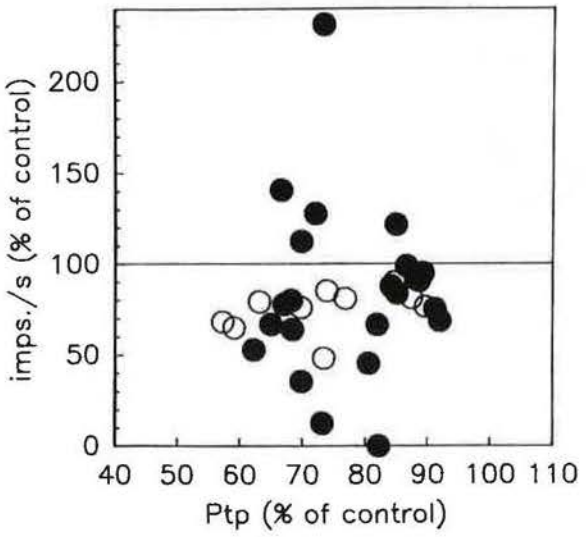

Fig. 3. – Effect of an increase in dynamic lung compliance on the peak rate of discharge of the SARs studied. Abscissa: transpulmonary pressure in percentage of control; ordinate: peak rate of discharge of SARs in the first breath following hyperinflation, as percentage of control; closed symbols: intrapulmonary receptors; open symbols: extrapulmonary receptors. All tracheal receptors and fourteen of the intrapulmonary receptors decreased their rate of discharge as dynamic compliance (as reflected by an opposite change in transpulmonary pressure) increased. Of the remaining SARs, four did not appreciably change their rate of discharge whilst five increased it.

the airways and SARs of the region be exposed to the changes in transpulmonary pressure as measured at the trachea. The presence of a respiratory modulated activity during the period preceding hyperinflation may depend on local phenomena of interdependence that are related to forces exerted by the surrounding ventilated parenchyma.

Once the lungs are hyperinflated the airways would open, the receptors would sense the overall pressure and change their discharge accordingly. To test this hypothesis in a few cases, the lobe in which a "normally" behaving receptor was located, was manually collapsed. During this procedure receptor discharge was reduced and in one case even ceased. After hyperinflation of the lobe the overall transpulmonary pressure decreased, but receptor activity increased (fig 4).

The relatively small number of SARs in which an increase in lung compliance led to an increase in peak rate of discharge could be indicative of the small proportion of peripherally located SARs [9]. It is of interest that behaviour similar to that of the majority of SARs, *i.e.* an inverse relationship between receptor activity and lung compliance, has been demonstrated for rapidly adapting airway receptors (RARs) [6,10]. A good example of the combined effect of changes in lung compliance on SARs and RARs is given by SELLICK and WIDDICOMBE [10] in their figure 1.

It has been postulated that the activitation of rapidly adapting receptors that occurs when pulmonary compliance decreases provides a triggering mechanism for spontaneously occurring augmented breaths that, by re-expanding the lung, reinstitute normal pulmonary distensibility [11]. Perhaps the diminished activity of those SARs located within collapsed portions of the lung also contributes to this mechanism. In fact, a reduction in SAR activity would result in a decreased inhibition of inspiration leading to deeper inspirations that would help to reopen collapsed airways. Implicit in this hypothesis is the assumption that peripherally located SARs have a greater influence on the pattern of breathing than SARs in more central airways. Some support for this hypothesis may be found in the report by NILSESTUEN *et al.* [12]. This aberrant behaviour of SARs would be more likely

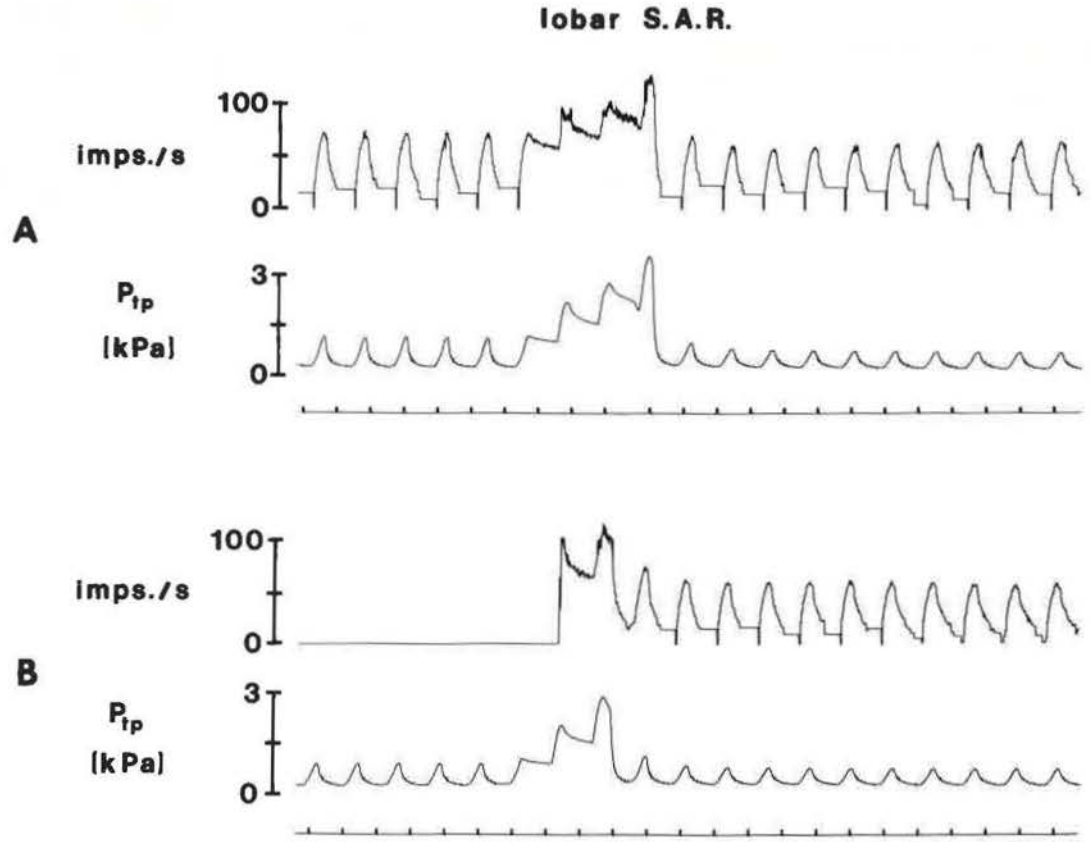

Fig. 4. – Activity of receptor localized in the lower lobe of the right lung. A: the peak activity of the receptor varied according to the changes in transpulmonary pressure, *i.e.* lower transpulmonary pressure=lower activity. B: trial performed after complete collapse of the lung lobe in which the receptor was located. After hyperinflation of the lungs the overall peak transpulmonary pressure at each breath was lower than before inflation. However, the receptor investigated was silent preceding the inflation and became active following it. Symbols as in Fig 1.

to occur in the newborn and elderly where tidal breathing is within the closing volume of the lung [13, 14].

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RÉSUMÉ: La pression transpulmonaire est considérée comme étroitement associée à l'activité des mécano-récepteurs à adaptation lente. La pression transpulmonaire, nécessaire à l'inflation pulmonaire jusqu'à un volume déterminé, dépend de la compliance pulmonaire :à des volumes courants égaux, une pression moindre sera nécessaire si la compliance est plus importante. Dès lors, on s'attend à une relation inverse entre l'activité des récepteurs et la compliance pulmonaire pour des modifications équivalentes du volume pulmonaire. Nous avons étudié les récepteurs de tension à adaptation lente chez 33 chiens anesthésiés, vagotomisés, paralyés et ventiles artificiellement, à

thorax ouvert, à un volume courant et à une fréquence constants. Après que l'on ait augmenté la compliance pulmonaire par l'hyperinflation, les 10 terminaisons trachéales étudiées et 14 des 23 récepteurs bronchiques intrapulmonaires étudiés, ont réduit leur activité. Des autres récepteurs intrapulmonaires, 5 ont augmenté leur activité et 4 sont restés inchangés. Nos résultats indiquent que, quoique la décharge des récepteurs de tension des voies aériennes soit plus souvent en relation avec la pression transpulmonaire, dans le cas de terminaisons à localisation périphérique, cette relation n'est pas toujours présente; ceci pourrait être dû à une divergence entre la pression transmurale locale et la pression transpulmonaire globale. Donc, à côté de l'indépendance bien décrite de l'activité des mécano-récepteurs à adaptation lente à l'égard des volumes pulmonaires, l'activité de ces mêmes récepteurs ne peut pas toujours être prédite sur la base des modifications de la pression transpulmonaire, lorsqu'ils ont une localisation périphérique.