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Influence of lung volume on histamine-induced bronchoconstriction in guinea-pigs

A.M. Lorino, M. Benichou, I. Macquin-Mavier, M.L. Franco-Montoya, H. Lorino, A. Harf

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ABSTRACT: The influence of lung volume on bronchopulmonary reactivity was investigated in 4 groups of 14 anaesthetized paralysed mechanically ventilated guinea-pigs: animals of group 1 served as control; in animals of group 2, the parasympathetic nervous system was blockaded with atropine; animals of group 3 were submitted to a bilateral cervical vagotomy; animals of group 4 were both vagotomized and pretreated with atropine. In each group, the animals were randomly divided into 2 subgroups: one was ventilated at zero end-expiratory pressure (ZEEP), the other with 0.2 kPa positive end-expiratory pressure (PEEP) resulting in a mean increase in lung volume of about 1 ml. Bronchopulmonary response to infused histamine was assessed by the respiratory conductance and compliance values measured during bronchoconstriction (respectively HGrs and HCrs).

In the control group, animals exposed to PEEP were found significantly less reactive than those ventilated at ZEEP. In groups 2, 3 and 4, this difference was significantly reduced for HGrs and even abolished for HCrs.

These results demonstrate that the effect of lung volume on moderate histamine-induced bronchoconstriction in guinea-pigs is not purely mechanical, but is partly vagally mediated. They also suggest that this vagally mediated inhibitory influence results from involvement of central reflexes evoked by stretch receptor stimulation.

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The influence of lung volume on respiratory mechanics in normal mammals has been widely studied. In general, in response to an increase in lung volume, both airway diameter and pulmonary and respiratory conductances have been found to increase [1–5], whereas dynamic lung compliance has been found to decrease [4]. By contrast, the effects of lung volume on respiratory response to bronchial challenge remain poorly documented. It has been demonstrated that a temporary increase in lung volume, either by positive end-expiratory pressure (PEEP) in mechanically ventilated cats [6], or by adjusting end-expiratory volume in spontaneously breathing subjects [7], limits maximal methacholine-induced bronchoconstriction. In both cases this limitation in maximal bronchoconstriction was explained by a purely mechanical effect [6, 7]. However it is well known that in most experimentally induced bronchoconstrictions, the parasympathetic system is clearly involved, and there is recent evidence that, in response to histamine, the vagal component is large at low levels of bronchoconstriction [8]. Consequently one may wonder whether, for mild bronchoconstriction induced by histamine, the limitation in airway narrowing due to increased lung volume is still attributable to a purely mechanical effect.

The purpose of the present study was to explore the mechanisms involved in the effect of lung volume on moderate bronchoconstriction induced by infused histamine. To investigate the possibility that this effect was vagally mediated, we assessed bronchoconstriction in animals mechanically ventilated from two end-expiratory volume levels, in the following conditions: no pretreatment, pretreatment with atropine and vagotomy, either singly or in combination.

Materials and methods

Animal preparation

We studied 56 male Hartley strain guinea-pigs with mean body weight 353±23 (SD) g, divided into 4

groups (n=14) to be pretreated differently (see Experimental procedure). Each animal was anaesthetized with pentobarbital (40 mg·kg^{-1} *i.p.*) and placed supine. A tracheal cannula was inserted, and a jugular venous catheter (internal diameter 0.3 mm) was placed for drug administration. The animals were then paralysed (vecuronium bromide 0.1 mg·kg^{-1} *i.v.*), and mechanically ventilated by a volumetric custom-made ventilator ensuring a constant inflation flow rate. The ventilatory frequency was 60 min^{-1}, the tidal volume 6 ml·kg^{-1}, and the inspiratory to expiratory duration ratio 2/3.

In each group, the animals were randomly divided into two subgroups (n=7). The animals of the first subgroup were ventilated with a zero end-expiratory pressure (ZEEP), and those of the second subgroup with a 0.2 kPa positive end-expiratory pressure (PEEP) inducing an increase of about 1 ml in the end-expiratory lung volume, which was consistent between animals. This increase in end-expiratory lung volume was measured at the end of the experiment, when respiratory mechanics had returned to their basal level, by displaying on a scope the volume signal before and after cessation of the PEEP. To prevent alveolar atelectasis in the animals under ZEEP conditions, a large inflation, to simulate a sigh, was performed every five minutes by occlusion of the expiratory valve for 3 respiratory cycles.

Respiratory compliance (Crs) and conductance (Grs) were measured 4 min after the deep inflations, and no inflation was performed during histamine infusion. Rectal temperature was monitored continuously and maintained constant by a heated blanket (Animal Blanket Unit, Harvard).

Experimental procedure

After a 10 min stabilization period, a first set of values for compliance Crs and conductance Grs of the respiratory system was estimated and taken as control values for all animals. Animals were then pretreated as follows: animals of group 1 received 0.1 ml saline *i.v.*; animals of group 2 were treated *i.v.* with 3 mg·kg^{-1} atropine; animals of group 3 were submitted to bilateral cervical vagotomy; animals of group 4 received 3 mg·kg^{-1} atropine *i.v.* and were vagotomized.

After another 10 min, a new set of values for Crs and Grs was estimated, and taken as basal values. Immediately afterwards, a histamine solution was administered intravenously *via* the jugular catheter as a continuous 5 min infusion, at a constant mass flow of 100 ng·kg^{-1}·s^{-1} for animals of group 1, 200 ng·kg^{-1}·s^{-1} for animals of groups 2 and 4, and 150 ng·kg^{-1}·s^{-1} for animals of group 3, in order to obtain the same level of bronchoconstriction under ZEEP conditions. When the mechanical parameters reached a plateau, respiratory compliance and conductance were measured again and later referred to as HCrs and HGrs respectively.

Determination of respiratory parameters

Tracheal pressure (P) was measured with a differential pressure transducer (Validyne MP45±5 kPa) connected to the tracheal cannula. Inspiratory flow ($\dot{V}$) was measured by a pneumotachograph (Fleisch # 000) connected to a differential pressure transducer (Validyne MP45±0.2 kPa). The equipment flow resistance was linear over the experimental flow range and amounted to 0.004 kPa·ml^{-1}·s.

Pressure and flow signals were low-pass filtered (second order, 8 Hz cut-off frequency), and then sampled at 32 Hz for 5 s by a 12-bit A-D converter (Gauthier, France). Samples were fed into an Apple II microcomputer. The two signals' baselines, corresponding respectively to barometric pressure and zero flow, were established before starting mechanical ventilation. P and $\dot{V}$ were then referenced to their baseline, and on line integration of $\dot{V}$ by the trapezoidal rule yielded the instantaneous inspiratory volume V.

Respiratory compliance and conductance measurement was based on the general equation of motion of the respiratory system:

$$P = (1/Crs)\cdot V+(1/Grs)\cdot \dot{V}_1$$

in which the term including V represents elastic pressure, and that including $\dot{V}$, resistive pressure. The method used in this study has been previously described [9]. In brief, during a constant flow inflation, compliance can be estimated as the inverse of the slope of the regression line of P on V, and conductance, as the ratio of the constant flow to the intercept of the regression line on the pressure axis corrected for positive end-expiratory pressure, if present. At the end of histamine infusion, and for each animal, the absence of intrinsic positive end-expiratory pressure (PEEPi) was verified as follows: the respiratory circuit was occluded at the end of the expiratory phase, and after a 2 s equilibration period, the tracheal pressure was measured and found equal to barometric pressure in the animals under ZEEP, and to the PEEP value in the animals under PEEP. For each cycle, automated data analysis was performed over the 40–90% range of inspiratory time, when both pressure and volume always varied linearly with time. The conductance values were corrected for that of the equipment. Values obtained for compliance and conductance were then averaged over each 5 s period of data acquisition.

Statistical analysis

Statistical analysis was performed using t-test for paired data, and analysis of variance completed as necessary by t-test for unpaired data.

Results

Control values are given in table 1. Respiratory compliance was similar in ZEEP and in PEEP animals,

whereas respiratory conductance was significantly higher in PEEP animals: PEEP induced a mean 60% increase in respiratory conductance ($p<0.001$).

After pretreatment, no significant difference was found between control and basal values of respiratory mechanics in each subgroup of groups 1, 2, 3 and 4.

Table 1 – Control values for respiratory compliance and conductance obtained in the 4 groups

	Group 1		Group 2		Group 3		Group 4	
	ZEEP	PEEP	ZEEP	PEEP	ZEEP	PEEP	ZEEP	PEEP
Crs ml·kPa^{-1}	4.0±0.4	3.9±0.4	4.1±0.3	3.9±0.4	4.0±0.4	4.0±0.4	4.0±0.5	3.9±0.4
Grs ml·kPa^{-1}	28±3	47±5*	29±3	46±7*	30±3	45±5*	30±3	46±4*

Mean values ±SD for control respiratory compliance, Crs, and conductance, Grs, obtained in each subgroup of the four groups (n=7). *: significantly higher than Grs value obtained in animals of the same group ventilated at ZEEP ($p<0.001$). PEEP: positive end-expiratory pressure; ZEEP: zero end-expiratory pressure.

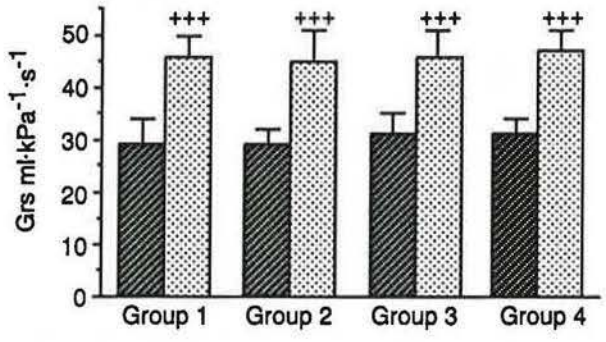

Fig. 1 – Respiratory conductance, Grs, obtained under basal conditions in animals ventilated at zero end-expiratory pressure (ZEEP) and with 0.2 kPa positive end-expiratory pressure (PEEP). Pretreatment was saline in group 1, atropine in group 2, vagotomy in group 3, and atropine plus vagotomy in group 4. Mean values (n=7 in each subgroup) and SD. +++: significantly higher than corresponding value measured in animals of the same group ventilated at ZEEP ($p<0.001$). ▬ : ZEEP; ▨ : PEEP.

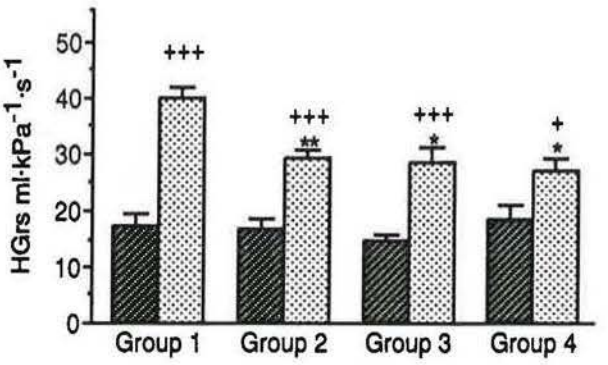

Fig. 2 – Respiratory conductance, HG_{rs} obtained during histamine-induced bronchoconstriction. Pretreatment as in Fig 1 legend. Mean values (n=7 in each subgroup) and SE. + and +++: significantly higher than HGrs value obtained in animals of the same group ventilated at zero end-expiratory pressure (ZEEP) ($p<0.05$ and 0.001, respectively), * and **: significantly lower than HGrs value obtained in animals of group 1 ventilated with positive end-expiratory pressure (PEEP) ($p<0.02$ and 0.01, respectively). ▬ : ZEEP; ▨ : PEEP.

In other words, none of these pretreatments abolished the PEEP-induced increase in respiratory conductance (fig. 1).

Under histamine infusion, the mean values obtained in group 1 for conductance, HGrs, and compliance HCrs (figs. 2 and 3), were found significantly higher under PEEP than under ZEEP conditions ($p<0.001$ for HGrs and $p<0.05$ for HCrs). In groups 2, 3 and 4, HGrs was also significantly higher in PEEP animals (fig. 2), whereas no significant difference was observed for HCrs (fig. 3). However, in PEEP animals of groups 2, 3 and 4, HGrs was significantly lower than in PEEP animals of group 1 (fig. 2).

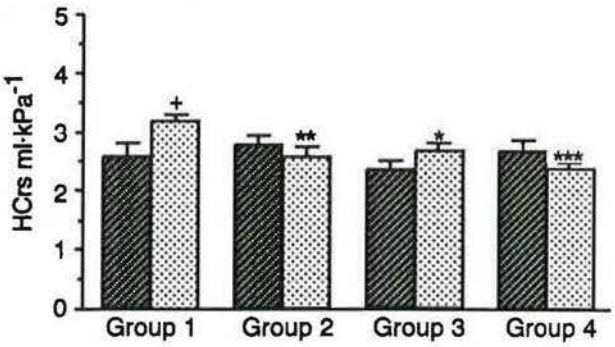

Fig. 3 – Respiratory compliance, HC_{rs} obtained during histamine-induced bronchoconstriction. Pretreatment as in Fig 1 legend. Mean values (n=7 in each subgroup) and SE. +: significantly higher than HC_{rs} value obtained in animals of the same group ventilated at zero end-expiratory pressure (ZEEP) ($p<0.02$). *, ** and ***: significantly lower than HCrs value obtained in animals in group 1 ventilated with positive end-expiratory pressure (PEEP) ($p<0.05$, 0.02 and 0.001, respectively). ▬ : ZEEP; ▨ : PEEP.

Discussion

The influence of lung volume (V_L) on maximal methacholine-induced bronchoconstriction has been studied in man [7] and cats [6], and characterized by a decrease in bronchoconstriction with increasing lung volume. Since the V_L influence was not abolished after cutting either the sympathetic or parasympathetic branches of the vagi, SLY *et al.* [6] concluded that the

reduction in bronchoconstriction caused by increasing lung volume is not neurally mediated, but rather related to an increase in the mechanical impedance due to airway smooth muscle shortening. Similarly, DING *et al.* [7] explained their results by a mechanical effect, and suggested that changes in lung volume act to alter the forces of interdependence between airways and parenchyma that oppose airway smooth muscle contraction. However, these two studies relate to maximal bronchoconstriction, and the conclusions proposed by their authors may become questionable for moderate bronchoconstriction. It has indeed been recently proved that the degree of bronchoconstriction is a determinant factor of the contribution of the different mechanisms to the bronchial responsiveness to histamine challenge [8], and that the vagal component, which is large at low levels of bronchoconstriction, becomes lesser at higher levels. Therefore, we decided to investigate the effects of increased lung volume on the response of respiratory mechanics to infused histamine during moderate bronchoconstriction *i.e.* when the parasympathetic system is largely involved, and to study the mechanisms underlying these effects.

Bronchoconstriction induced by histamine is due to an increase in the tone of airway smooth muscle, which mainly results from both a direct action on H_1 receptors and a vagovagal reflex evoked by stimulation of subepithelial irritant receptors. This vagal reflex may be attenuated by involvement of the tracheobronchial slowly adapting stretch receptors [10] which enhance their activity when lung volume is increased [11] or when histamine is administered [12]. The inhibitory innervation of airways comes from two sources, the sympathetic system, which has a modulatory influence on cholinergic neurotransmission within parasympathetic ganglia [13, 14] and the nonadrenergic inhibitory system [15, 16], which might be stimulated during bronchoconstriction in animals exposed to PEEP, resulting in an enhanced inhibitory neural control. In this study, an attempt was made to investigate the action of PEEP on bronchoconstriction, and more particularly to determine the role of the cholinergic system in this action.

In this work we used respiratory parameters to study the PEEP influence on pulmonary compliance and conductance in the basal state and during histamine-induced bronchoconstriction. This choice was previously justified in ZEEP guinea-pigs whose chestwall compliance and conductance are markedly higher than their pulmonary compliance and conductance [17]. It may be considered still valid in PEEP animals whose chestwall compliance remains unchanged, and whose chestwall conductance tends to increase with increasing lung volume. It has been documented that tissue resistance could contribute a large proportion of overall lung resistance and vary with lung volume [18]. In guinea-pigs, PEEP rather tends to decrease tissue resistance [4]. Furthermore LUDWIG *et al.* [19] have recently demonstrated that, in response to histamine, there were a significant correlation between changes in airway and tissue resistance, and a similar sensitivity of the tissues and airways. Therefore, in the present study, respiratory conductance probably remains a good index of airway conductance.

Control and basal conditions

As previously reported [4], the control values for respiratory compliance were found similar in ZEEP and in PEEP animals (table 1). The establishment of the PEEP resulted in a marked increase in respiratory conductance (table 1). These results are in agreement with those reported for airway, pulmonary or respiratory conductance in guinea-pigs [4] and dogs [2, 3, 5], but at variance with those reported by LUDWIG *et al.* [18] in dogs. The VL-induced changes in respiratory conductance may be explained by a purely mechanical effect on airway conductance. Indeed, at higher lung volume, the elastic recoil pressure and thus the airway transmural pressure is increased.

After atropine pretreatment or vagotomy, the VL influence on Grs remained unchanged (fig. 1). These results, similar to those of WATSON *et al.* [4], demonstrate that the effect of lung volume on respiratory conductance is not vagally mediated, probably because the airway smooth muscle tone is very low in anaesthetized guinea-pigs. So, the VL influence on Grs seems to only result from a purely mechanical effect, contrary to that observed in dogs [1, 2, 3, 5].

Histamine infusion

As parasympathetic blockade decreases sensitivity [14, 20, 21], the dose of infused histamine was adjusted according to the pretreatment in order to obtain, in all ZEEP animals, similar levels of bronchoconstriction, *i.e.* similar values of HCrs and HGrs. In this way, an inter-group comparison was possible for the PEEP animals. It is highly improbable that non-smooth muscle related mechanisms were involved in the effects of PEEP observed in the present study. Indeed, oedema results in a decrease in compliance, and in all our animals, compliance returned to basal level after histamine infusion was stopped.

In the control group, when compared to ZEEP animals, PEEP animals exhibited significantly less bronchoconstriction in response to infused histamine (figs. 2 and 3). As the basal values of Crs were similar in both subgroups, the higher values of HCrs observed in PEEP animals reflect a true reduction in bronchopulmonary reactivity. This reduction was more marked for HGrs (fig. 2) than for HCrs (fig. 3), which suggests that the bronchodilating effect of PEEP acts more markedly on central airways than on peripheral airways. Indeed compliance changes rather reflect events occurring in the peripheral airways, whereas conductance changes mainly reflect events occurring in the central airways [21, 22].

After atropine pretreatment, the VL influence on HGrs was significantly reduced (fig. 2) and that on

HCrs was abolished (fig. 3), which demonstrates that the PEEP-induced limitation of bronchoconstriction is not due to a purely mechanical effect, but is partly vagally mediated. In order to determine whether this vagally mediated inhibitory influence results from a central reflex evoked by the stretch receptor stimulation, and/or a local action of sympathetic nerves on cholinergic neurotransmission within parasympathetic ganglia, two other groups of animals submitted respectively to vagotomy and vagotomy plus atropine pretreatment were studied.

After bilateral vagotomy, the V_L influence was significantly reduced for HGrs (fig. 2), and abolished for HCrs (fig. 3). Our observations differ from those of SLY *et al.* [6] who evidenced no significant change in the effect of lung volume on methacholine induced maximal bronchoconstriction in cats after vagotomy. However, it must be emphasized that these authors studied another animal species in different experimental conditions. Indeed, in contrast to acetylcholine, histamine stimulates irritant receptors directly and therefore evokes a greater reflex component in the airway response than acethylcholine [23]. Furthermore, contrary to guinea-pigs challenged with histamine, cats challenged with methacholine are more reactive after parasympathectomy [24], which perhaps illustrates the role of the non adrenergic inhibitory system. Lastly, the contribution of the different mechanisms involved in the mediation of bronchoconstriction varies with the level of bronchoconstriction [8].

Comparison between PEEP animals of groups 2 and 3 shows that atropine and vagotomy similarly reduce the V_L influence on histamine-induced bronchoconstriction (figs. 2 and 3). However, to demonstrate that this influence results from a central vagal reflex evoked by the stretch receptor stimulation, we must exclude the simultaneous involvements of the sympathetic modulation of the parasympathetic ganglia and of the action of the non adrenergic inhibitory system (NAIS). We investigated the role of sympathetic modulation by comparing to group 3 a fourth group of animals, vagotomized and pretreated with atropine. As no significant difference was observed between HGrs or HCrs in PEEP animals of groups 3 and 4 (figs. 2 and 3), we can conclude that the sympathetic modulation, and consequently the NAIS, are not involved in the V_L influence on bronchoconstriction.

The major finding in this study is that the V_L influence on moderate histamine-induced bronchoconstriction is partly vagally mediated *via* central reflexes. This finding, which differs from those reported for maximal methacholine induced bronchoconstriction [6, 7], is consistent with the important role of central vagal reflexes in the mediation of moderate histamine induced bronchoconstriction. The role of slowly adapting stretch receptors in the regulation of airway smooth muscle tone has been widely studied in many species [10]. Such receptors have been recently identified in guinea-pigs where the majority of them have been demonstrated to be localized in small airways and in lung parenchyma [25]. Silent in the basal state if inflation does not reach a critical level, they increase their activity in response to histamine infusion thus promoting bronchodilatation in preconstricted smooth muscle [12]. Our results tend to prove that a small increase in lung volume does not affect the activity of stretch receptors in the basal state, but considerably enhances it when airway smooth muscle is constricted by histamine.

Since the V_L influence was not completely abolished after parasympathetic blockade, it is more than likely that a mechanical effect has contributed to the decreased bronchoconstriction observed in PEEP animals. Indeed, in groups 2, 3 and 4, the elastic recoil pressure, and therefore the airway transmural pressure, were, compared to ZEEP animals, higher in PEEP animals who had identical HCrs values and increased lung volumes.

In conclusion, this study presents new observations on the influence of lung volume on moderate bronchoconstriction in response to infused histamine in guinea-pigs. Although other potential mechanisms cannot be really excluded, the PEEP-induced decrease in bronchoconstriction appears to mainly result from both a purely mechanical effect and a vagally mediated inhibitory influence which suggests involvement of central reflexes evoked by stretch receptor stimulation.

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Influence du volume pulmonaire sur la bronchoconstriction induite par l'histamine chez le cobaye. A.M. Lorino, M. Benichou, I, Macquin-Mavier, M.L. Franco-Montoya, H. Lorino, A. Harf.

RÉSUMÉ: L'influence du volume pulmonaire sur la réactivité bronchopulmonaire à l'histamine a été étudiée sur 4 groupes de 14 cobayes anesthésiés, curarisés et ventilés mécaniquement. Les animaux du groupe 1 ont reçu du sérum physiologique, ceux du groupe 2 de l'atropine, ceux du groupe 3 ont été vagotomisés, et ceux du groupe 4 prétraités par atropine et vagotomisés. Les animaux de chaque groupe ont été ensuite répartis de façon aléatoire en 2 sous groupes. Les animaux du premier sous groupe étaient ventilés avec une pression télé-expiratoire nulle (ZEEP), ceux du second avec une pression télé-expiratoire positive (PEEP). La PEEP, d'une valeur de 0.2 kPa, entrainait une augmentation moyenne d'environ 1 ml du volume pulmonaire. La réponse bronchopulmonaire à une perfusion d'histamine était évaluée par les valeurs de compliance et de conductance respiratoires mesurées au cours de la bronchoconstriction. Dans le groupe 1, une différence significative du degré de bronohoconstriction a été observée entre les deux sous groupes, la bronchoconstriction étant moindre chez les animaux en PEEP. Comparativement au groupe 1, dans les groupes 2, 3, et 4, cette différence était réduite de façon significative en termes de conductance, voire même abolie en termes de compliance. Ces résultats montrent qu'une augmentation du volume pulmonaire réduit la bronchoconstriction induite par l'histamine, et ce par un double effet, mécanique et vagal. L'influence inhibitrice vagale, qui met en jeu un réflexe central, résulte vraisemblabement de la stimulation des récepteurs pulmonaires à l'étirement.
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