

Mechanisms of hyperinflation in asthma

Y. Cormier*, R. Lecours, C. Legris

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ABSTRACT: We studied 11 mild asthmatics to verify whether the mechanisms of hyperinflation in asthma could be inhibited or overcome by passively changing lung volumes. On day 1, we induced a fall in forced expiratory volume in one second (FEV₁) of 30-60% by methacholine inhalation and measured the resulting increase in FRC (Δ FRC). The Δ FRC was 729 \pm 378 ml (mean \pm SD). On day 2, with the subject supine in an iron lung, we measured oesophageal (Poes), gastric (Pgas) and transdiaphragmatic (Pdi) pressures, and changes in functional residual capacity (FRC) (Δ V) induced by extrathoracic pressures from -20 to +20 cmH₂O before and after bronchoprovocation. With positive pressures, the FRC decreased and reached a plateau at 10 cmH₂O pressure or higher. This plateau was at a mean FRC of 839 ml higher after the bronchoprovocation than before. Pdi at FRC varied in the same direction as the extrathoracic pressure and was not modified by the bronchospasm. Peak inspiratory Pdi, without pressure applied in the iron lung, increased from 13.6 \pm 5.4 to 28.1 \pm 13.5 cmH₂O after methacholine; extrathoracic pressure of -20 cmH₂O decreased this latter value to 15.4 \pm 7.3 cmH₂O (p<0.01). The increased lung volume and the displaced chest wall recoil curve after provocation were not inhibited by positive or negative extrathoracic pressures. Our data show that the mechanisms of hyperinflation are not eliminated or overcome by passively changing lung volumes and support the hypothesis that persisting activity of inspiratory muscles other than the diaphragm during expiration and perhaps a prolonged expiratory time constant are responsible for hyperinflation in asthma.

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Asthma is characterized by an increase in airways resistance and in lung volumes. The degree of hyperinflation is usually correlated with the severity of the bronchospasm. Values for functional residual capacity (FRC) as high as the pre-bronchospasm total lung capacity (TLC) have been described [1, 2]. Although this phenomenon is well known, the mechanisms by which this hyperinflation is achieved are still hypothetical. Previous studies have described a persistent inspiratory muscle activity and glottic constriction during expiration in asthmatics during bronchospasm and in normals under resistive loading [3-9]. It has also been suggested that airway closure [10, 11] and prolonged time constant could contribute to this hyperinflation.

The increase in lung volume has the potential physiological advantage of dilating airways and increasing elastic recoil pressure. Potential disadvantages also exist, however; increased FRC adds to the inspiratory elastic load and, furthermore, if this increase in FRC is accomplished by persistent inspiratory muscle contraction during expiration, it may lead to

inspiratory muscle fatigue. Studies of the hyperinflation mechanisms have led to the suggestion that asthma attacks could be treated by continuous positive airway pressure (CPAP) [12]. This could be helpful both by maintaining airways open and by taking over the hyperinflation, therefore releasing the need for inspiratory muscle contraction and retarding muscle fatigue.

The present study was carried out for two purposes. Firstly, we wanted to see if hyperinflation induced by bronchospasm could be countered by applying negative extrathoracic pressure or if this negative pressure would only lead to further hyperinflation. Secondly, whether hyperinflation could be counterbalanced by positive extrathoracic pressure. We studied eleven mild asthmatics in an iron lung, before and after methacholine bronchoprovocation and found that negative extrathoracic pressure does not shut-off the mechanism of hyperinflation, but leads to further lung expansion. Also, positive extrathoracic pressure cannot eliminate all the hyperinflation.

Material and methods

Study population

Eleven mild asthmatics, 5 males and 6 females, were selected for this study. The diagnosis of asthma was based on the American Thoracic Society criteria [13]. All had clinically stable asthma and took aerosolized β_2 -agonist as required. One subject also received regular beclomethasone treatment. The concentration of methacholine giving a 20% drop in forced expiratory volume in one second ($PC_{20}FEV_1$) ranged from 0.06–8 mg·ml⁻¹. The protocol was approved by our institution's Ethics Committee, and each volunteer signed a consent form prior to the study.

Study protocol

Each subject was seen twice. On the first visit, the subjects having withheld their β_2 -agonists for at least 8 h, we measured the baseline FEV_1 and supine FRC by helium dilution. We then did a methacholine challenge as described previously [14]. Once an FEV_1 drop of 20% or more was achieved, the supine FRC was remeasured. Spirometry was performed with a Collins Stead-Wells 06041 spirometer (Braintree MA). Helium volume measurements were obtained with a helium residual volume apparatus (Warren E. Collins, Braintree MA).

Each volunteer was studied on a second day within one week of day 1. On this visit we measured the subject's FEV_1 , and positioned two oesophageal balloon catheters, one in the lower oesophagus and one in the stomach. A control FEV_1 was obtained to assure that this manoeuvre had not modified the subject's airways. The subject was laid down in an iron lung and was connected, by a mouthpiece, to the Collin's spirometer through a closed circuit containing a CO₂ scrubber and filled with 100% O₂. A noseclip was also secured. The tubings of the oesophageal and gastric balloons were connected to Validyne pressure transducers (MP45-1-871)

to obtain oesophageal pressure (Poes), gastric pressure (Pgas) and transdiaphragmatic pressure (Pdi). The transducer signals were played into a Validyne CD101-871 paper recorder (Engineering Corporation, CA). We then applied continuous negative or positive pressure in the iron lung to inflate and deflate the subject's lungs. This was done by suctioning or blowing air into the iron lung by means of a vacuum cleaner. Pressures were set at 0, -5, -10, -15, -20, 0, +5, +10, +20 cmH₂O. At each pressure, sufficient time was allowed to obtain stable values for changes in lung volume (ΔV) as read on the spirometer, breathing frequency (fb), tidal volume (V_T), Poes, Pgas and Pdi. After these manoeuvres, the subject was taken out of the iron lung and another control FEV_1 was obtained. A methacholine dose equal to the maximum given on day 1 was nebulized and FEV_1 was measured. Following this, the subject was returned into the iron lung, the same pressures were applied and the same measurements made. We further increased the iron lung pressure to +30 cmH₂O in 3 subjects and measured expiratory reserve volume (ERV) at this level, both before and after the methacholine challenge. At the end of the second series of tests, a final FEV_1 measurement was made and the subject was given an aerosol of β_2 -agonist to reverse the induced bronchospasm.

The increase in FRC induced by the bronchospasm was not remeasured on day 2; we took the values obtained on day 1 as a representative of ΔFRC of day 2. Negative pressure measurements were obtained for all 11 subjects; however, positive pressures were applied only in 9.

Results

Results of lung volumes and changes induced by methacholine challenge are given in table 1. The methacholine-induced bronchospasm resulted in an increased FRC in all subjects, with an increase 729 ± 378 ml (mean \pm SD). Baseline FEV_1 on both days of study was

Table 1. – Results of lung volume measurements before and after bronchoprovocation

Subjects	TLC pre	TLC post	VC pre	VC post	FRC pre	FRC post	RV pre	RV post
1	4.60	-	3.02	-	2.42	2.92	1.58	-
2	6.59	7.17	4.20	3.45	3.12	4.56	2.39	3.72
3	4.29	5.62	2.88	3.54	2.04	2.75	1.41	2.08
4	4.85	5.01	2.97	2.68	2.32	2.93	1.88	2.33
5	4.57	4.43	3.18	1.98	2.29	2.81	1.39	2.45
6	5.23	5.75	3.54	2.53	2.12	3.49	1.69	3.22
7	5.29	3.85	3.50	2.10	1.88	2.35	1.79	1.75
8	6.53	6.63	4.30	3.22	3.35	3.68	2.23	3.41
9	7.03	7.97	4.69	5.52	3.31	3.76	2.34	2.45
10	6.59	6.56	5.12	4.74	2.40	3.00	1.47	1.82
11	6.58	7.02	4.71	3.64	2.80	3.82	1.87	3.38
Mean \pm SD	5.65 \pm 1.02	6.00 \pm 1.30	3.83 \pm 0.80	3.34 \pm 1.12	2.55 \pm 0.52	3.28 \pm 0.64	1.88 \pm 0.36	2.66 \pm 0.71

Pre: before methacholine; post: after the challenge; TLC: total lung capacity; VC: vital capacity; FRC: functional residual capacity; RV: residual volume.

Table 2. - Individual results of the forced expiratory volume in one second (FEV₁)

Subjects	FEV ₁ B1 l	FEV ₁ P1 l	FEV ₁ B2 l	FEV ₁ P2 l	FEV ₁ P2 pre I.L. l	FEV ₁ P2 post I.L. l
1	2.02	1.14	1.80	1.20	1.22	1.45
2	2.86	1.79	3.12	2.07	2.05	2.04
3	2.74	1.90	2.55	1.36	1.30	1.52
4	2.45	1.64	2.62	1.95	1.95	1.97
5	2.73	1.85	2.05	1.30	1.30	1.24
6	2.00	1.43	2.29	1.25	1.20	1.55
7	2.65	1.17	2.78	1.59	1.19	1.60
8	3.08	1.83	2.87	1.65	1.29	1.72
9	3.55	2.38	3.46	2.39	2.26	1.59
10	3.67	2.25	3.96	2.56	1.84	2.06
11	3.29	1.49	3.10	1.61	1.44	1.47
Mean±SD	2.88±0.55	1.75±0.40	2.78±0.62	1.72±0.46	1.55±0.39	1.65±0.26
	p=0.66		p=0.95		p=0.28	

BI: baseline day 1; P1: post-challenge day 1; B2: baseline day 2; P2: post challenge day 2; P2 pre I.L.: after methacholine, supine in the iron lung before the application of negative and positive extrathoracic pressures; P2 post I.L.: at the end of the iron lung studies.

similar (table 2) ($p=0.66$). FEV₁ post-methacholine were also similar for both days ($p=0.95$). The bronchospasm persisted throughout the study (table 2).

Changing extrathoracic pressure in the iron lung did not change tidal volume. Breathing frequency remained similar for all negative pressures but significantly increased at +10 and +20 cmH₂O pressure ($p<0.01$).

Lung volume changes produced by iron lung pressures before and after methacholine bronchoconstriction are presented in figure 1. The slope of volume changes (ΔV) induced by negative iron lung pressures were significantly lower after methacholine provocations, than before ($p<0.01$) (fig. 1). However, the lung volume always remained higher after provocation than before the challenge. On the positive pressure side, if one considers the actual FRC values (upper line, fig. 1) it can be seen that FRC remained significantly higher throughout the pressure changes ($p<0.05$). The FRC reached a plateau at positive pressures between 10 and 20 cmH₂O. ERV at +30 cmH₂O increased after the methacholine challenge in all 3 subjects in whom it was measured (from 480 to 690 ml, 400 to 700 ml, and 350 to 500 ml).

The transdiaphragmatic pressure at both FRC and at the maximal inspiratory values are presented in figures 2 and 3. At FRC, both before and after methacholine challenge, negative iron lung pressure resulted in a progressively decreasing Pdi. This pressure difference increased under positive extrathoracic pressures.

The peak inspiratory Pdi (highest Pdi during a spontaneous breathing cycle) was increased by the induced bronchospasm from 13.6 ± 5.4 to 28.1 ± 13.5 cmH₂O at zero iron lung pressure (*i.e.* atmospheric pressure) ($p<0.01$). With the thoracic compression by positive iron lung pressures, this value showed a parallel increase both before and after methacholine. Before the provocation,

negative pressures had no influence on maximal Pdi. Negative pressures progressively decreased this value after bronchoprovocation from 28.1 ± 13.5 to 15.4 ± 7.3 cmH₂O at -20 cmH₂O iron lung pressure ($p<0.01$).

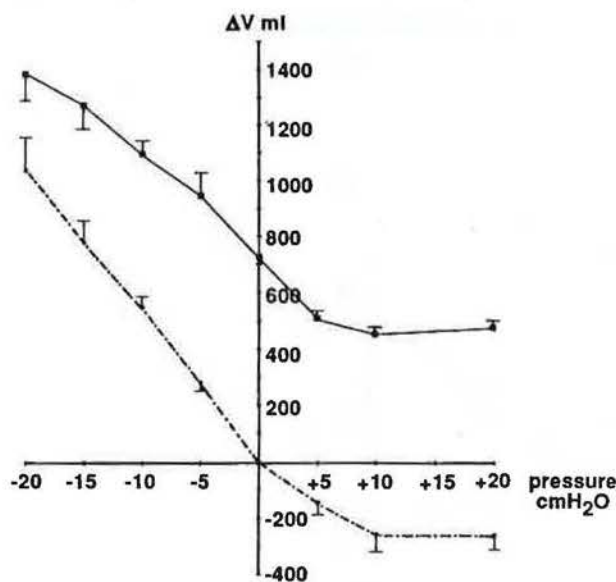


Fig. 1. - The x axis represents the extrathoracic pressures applied in the iron lung and the y axis the resulting change in FRC (ΔV). The lower line represents the mean \pm SEM values before the bronchoprovocation. For the ΔV values after the methacholine challenge (upper line) we have added the Δ FRC measured by helium dilution on day 1. Note that on the negative side the post-methacholine curve is less steep than the pre-methacholine value ($p<0.01$). On the positive pressure side an FRC plateau is reached between +10 and +20 cmH₂O pressures, both before and after challenge; this plateau however is seen at a much higher FRC in the presence of the induced bronchospasm ($p<0.05$). FRC: functional residual capacity; SEM: standard error of mean. ●—●: pre-methacholine; ■—■: post-methacholine.

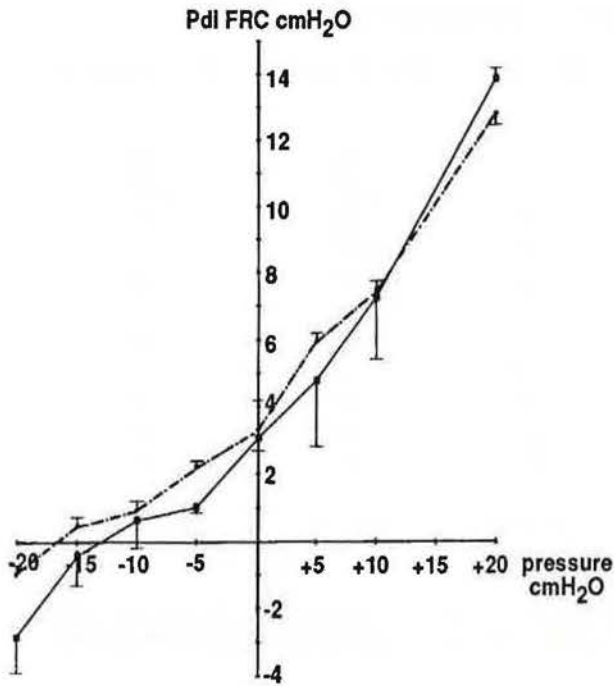


Fig. 2. - Transdiaphragmatic pressure (Pdi) at functional residual capacity (FRC), values given both for before and after methacholine challenge measured at each 5 cmH₂O pressure step from -20 to +10 cmH₂O and at +20 cmH₂O. Pdi changed in the same direction as the iron lung pressure and was not modified by the bronchoconstriction. ●- - - -●: pre-methacholine; ■- - - -■: post-methacholine.

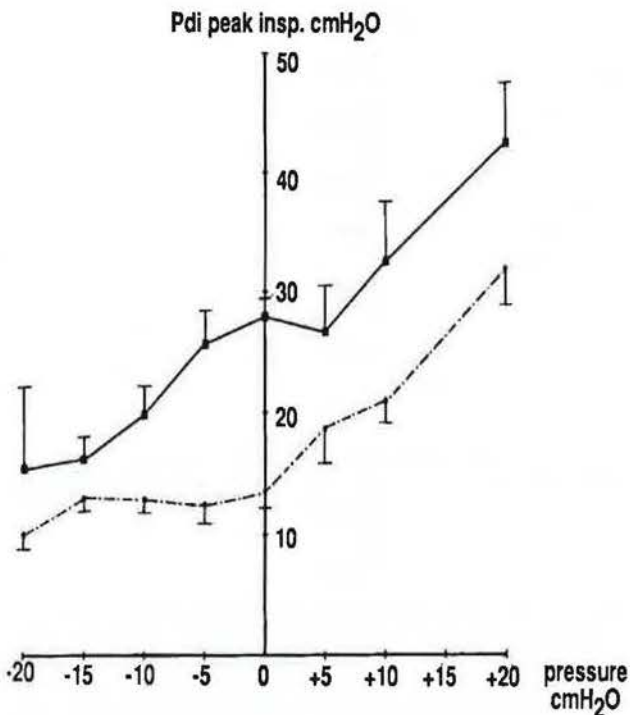


Fig. 3. - Maximal inspiratory Pdi during spontaneous breathing before and after methacholine challenge. Before the bronchospasm, negative pressure did not modify the pressure; however, it was significantly decreased ($p < 0.01$ at -20 cmH₂O) after the challenge. Positive iron lung pressure increased the inspiratory Pdi in a parallel fashion. ●- - - -●: pre-methacholine; ■- - - -■: post-methacholine.

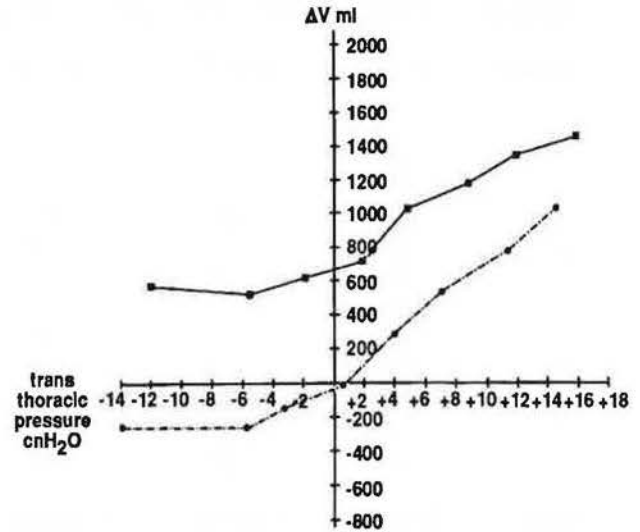


Fig. 4. - Transthoracic pressure in cmH₂O (oesophageal pressure - iron lung pressure) at the end of spontaneous expiration (FRC) both before and after methacholine bronchoprovocation at different lung volume changes (ΔV) induced by the iron lung pressures and by the bronchospasm itself. This pressure was less for any given lung volume after the bronchial challenge. This is consistent with an inspiratory muscle contraction persisting at the end of expiration. ●- - - -●: pre-methacholine; ■- - - -■: post-methacholine.

Trans thoracic pressures at FRC, representing the difference between Poes and iron lung pressure, are shown in figure 4. These values are plotted against ΔV . It can be seen that, at given lung volume, trans thoracic pressure was always lower after methacholine. The iron lung pressures changed the trans thoracic pressures along the pressure-volume (PV) characteristic of the thoracic cage. This PV curve after methacholine, although shifted, was parallel to the pre-challenge values. For any given lung volumes the recoil pressures of the thoracic cage are less after bronchoprovocation than at baseline values.

Discussion

We believe that the data from our study support the hypothesis that a prolonged expiratory time constant and persistent inspiratory muscle activity are involved in the hyperinflation seen with induced airway obstruction. Our data also show that the mechanisms of hyperinflation cannot be overcome by a passive hyperinflation or thoracic compression.

ΔFRC on day 2 was assumed to be equivalent to that measured on day 1. Although this may be criticized, since the FEV₁ fall on day 1 and day 2 were very similar (table 2), we believe it is probable that ΔFRC were also alike. Helium dilution technique tends to underestimate FRC in the presence of a bronchospasm; in this case any error introduced in ΔFRC by our measurement technique would tend to increase the significance of our findings. We used helium dilution instead of plethysmography because we wanted to measure ΔFRV in a supine position, the position in which subjects were studied in the iron lung.

With the application of negative and positive extrathoracic pressure, the lung volume always remained higher after the bronchoprovocation than before the challenge. This shows that the mechanisms of hyperinflation were not eliminated by our manoeuvre. The fact that FRC reached a plateau at a higher volume after the challenge could be explained by either an airway closure, a prolonged time constant, or muscle contraction. Since subjects could voluntarily further decrease their FRC at the high positive extrathoracic pressures, closure of all airways cannot be responsible for the increased FRC in this condition. A prolonged expiratory time constant is compatible with these observations. Inspiratory muscle activation would have to decrease with increasing positive extrathoracic pressure to keep a plateau FRC. We therefore believe that inspiratory muscle activation is an unlikely explanation for the higher FRC plateau after the methacholine provocation.

The slope of the relationship between negative extrathoracic pressure and lung volume was steeper before provocation than after. This could be explained by either a stiffer thoracic cage (due to increased muscle contraction?), a less compliant lung (due to its higher volume), or a progressive decrease in the contribution of the inspiratory muscles to the increased lung volume as the lung is passively inflated. Whatever the explanation, the lung volumes always remained higher under the bronchospasm, therefore the mechanisms of hyperinflation were not turned off by a passive inflation. This is further supported by the observation made on figure 4. After the methacholine challenge, the transthoracic pressure always remained lower for a given lung volume. Since one would not expect large changes in lung recoil with provocation and since any changes in thoracic wall compliance would come from muscle contraction, this lower transthoracic pressure adds evidence that more inspiratory muscle activation is present after methacholine provocation. The upper position of the post-methacholine curve in figure 4, shows that this lower transthoracic pressure is maintained over a large range of end-expiratory lung volume induced by the application of negative or positive extrathoracic pressure.

If we take a point at isovolume on figure 4, for example ΔV of 600 ml, the transthoracic pressure before methacholine is 7 cmH₂O while after methacholine it is -2 cmH₂O. This 9 cmH₂O pressure difference, we believe, can only be explained by inspiratory muscle contraction.

Pdi at FRC was not modified by the bronchoprovocation and the resulting hyperinflation. This suggests that the diaphragm does not play an important role in the hyperinflation as previously suggested [6]. However, this differs from the results of MUELLER *et al.* [9]. We have no explanation for this difference. The change in Pdi with changing extrathoracic pressure probably represents a difference in the transmission of iron lung pressure to the abdomen and the intrathoracic oesophagus. The behaviour of this pressure was no different before and after the provocation.

The increase in peak inspiratory Pdi after

bronchoprovocation is logical in the face of an increased inspiratory work load imposed by the bronchospasm. Passively increasing and decreasing lung volume, probably modified peak inspiratory Pdi mostly by its effect on lung volume dependent airway resistances. The lack of a decrease in Pdi with lung inflation before the provocation suggests that any decrease in airway resistance in this condition was counterbalanced by an increased inspiratory elastic load.

We conclude that active mechanisms involved in hyperinflation cannot be eliminated or overcome by passively increasing or decreasing the lung volume during an induced bronchospasm. Our data support the hypothesis that contraction of inspiratory muscles other than the diaphragm during expiration and probably a prolonged expiratory time constant are involved in the hyperinflation seen in the presence of a bronchospasm.

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Mécanismes de l'hyperdistension dans l'asthme. Y. Cormier, R. Lecours, C. Legris.

RÉSUMÉ: Nous avons observé 11 asthmatiques légers pour vérifier si les mécanismes d'hyperdistension de l'asthme pouvaient être inhibés ou contrôlés par une modification passive des volumes pulmonaires. Au jour 1, nous avons provoqué une chute de 30 à 60% du VEMS par inhalation de methacholine et avons mesuré l'augmentation de CRF (Δ CRF) qui en résultait. La Δ CRF atteignait 729 ± 378 ml (moyenne \pm DS). Au jour 2, le sujet étant en décubitus dans un poumon d'acier, nous avons mesuré les pressions oesophagienne (Poes), gastrique (Pgas) et transdiaphragmatique (Pdi) ainsi que les modifications de CRF (Δ V) induites par des pressions extrathoraciques de -20 à +20 cmH₂O, avant et après la provocation bronchique. Sous les pressions positives, la CRF diminue pour atteindre un plateau aux pressions de +10 cmH₂O ou davantage. Ce plateau se situe à un niveau moyen de CRF supérieur de 839 ml après bronchoconstriction par rapport à la

valeur avant bronchoconstriction. Pdi à la FRC évolue dans le même sens que la pression extrathoracique et n'est pas influencé par le bronchospasme. La Pdi inspiratoire de pointe, sans application de pression par le fœtus d'acier, passe de 13.6 ± 5.4 à 28 ± 13.5 cmH₂O après methacholine, une pression extrathoracique de -20 cmH₂O abaisse cette dernière valeur à 15.4 ± 7.3 cmH₂O ($p < 0.01$). L'augmentation de volume pulmonaire et le déplacement du recule des parois thoraciques après provocation ne sont pas inhibés par les pressions extrathoraciques positives ou négatives. Nos observations démontrent que les mécanismes de l'hyperdistension ne sont pas éliminés ou contrôlés par la modification passive des volumes pulmonaires; elles soutiennent l'hypothèse selon laquelle la persistance d'une activité de muscles respiratoires autres que le diaphragme pendant l'expiration, et peut être un prolongement de la constante de temps expiratoire, sont responsables de l'hyperdistension dans l'asthme.

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