Comparative effects of volume history on bronchoconstriction induced by hyperventilation and methacholine in asthmatic subjects

J-L. Malo, J. L'Archevêque, A. Cartier

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ABSTRACT: The aim of this study was to find out if bronchodilatation following deep inspiration can be induced by the inhalation of a "natural" stimulus (hyperventilation of cold dry air), and if the effect is similar to that induced by methacholine. After baseline assessment of lung resistance (R_L), 10 asthmatic subjects were asked to inhale cold dry air for 3 min. R_L was monitored continuously for 3–4 min, at which time subjects were asked to take a fast deep inspiration. After recovery, the manoeuvre was repeated and R_L was reassessed. The manoeuvre was then repeated a third time. After functional recovery, progressive doses of methacholine were inhaled until the increase in R_L was comparable to that obtained after hyperventilation ($56\pm16\%$ and $65\pm24\%$, respectively, mean±SD, NS). The same deep inspiration manoeuvre was repeated three times with recovery as after hyperventilation of cold dry air. Maximum changes in R_L were not significantly different after each of the three manoeuvres for either type of bronchoconstriction. The mean fall in R_L was $14.2\pm9.9\%$ after hyperventilation and $16.4\pm10.5\%$ after methacholine. There was a satisfactory correlation ($r=0.80$, $p<0.01$) between the bronchodilatation after deep inspiration for both types of stimuli. We conclude that the bronchodilator effect of deep inspiration is no different using either a pharmacological stimulus (methacholine) or a "natural" stimulus (hyperventilation of unconditioned air). These results show that assessing the response to hyperventilation with manoeuvres requiring deep inspiration, forced expiratory volume in one second (FEV_1) may alter airway tone in a way similar to pharmacological stimuli.
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Dept of Chest Medicine, Hôpital du Sacré-Coeur, Montreal, Canada.

Correspondence: J-L. Malo, Dept of Chest Medicine, Hôpital du Sacré-Coeur, 5400 W. Gouin, Montreal, Canada H4J 1C5.

Although the bronchomotor effect of deep inspiration on baseline airway tone is variable, most researchers have documented bronchodilatation in a situation of induced bronchoconstriction. The bronchodilator effect of deep inspiration after induced bronchoconstriction has been primarily documented using pharmacological agents. However, a group in Boston [1, 2] has shown that it can also be observed using a natural stimulus such as unconditioned air.

In this study, we have investigated asthmatic subjects to see if the bronchodilator effect of deep inspiration was similar using a pharmacological agent (methacholine) and hyperventilation of cold dry air.

Material and methods

Subjects

Ten adult subjects who satisfied the criteria for the diagnosis of asthma [3] were included in the study. All were in a stable state as judged by clinical criteria (no nocturnal awakening due to asthma, no recent need for extra medication). Atopic subjects had not been recently exposed to any antigens (pollens, animal danders) except for house dust. None of the subjects had suffered a recent (≤ 2 months) respiratory infection. Bronchodilators were stopped within the interval recommended by the American Academy of Allergy, 8 h for inhaled beta$_2$-adrenergic agents and 48 h for sustained-release theophylline derivatives [4]. Use of inhaled beclomethasone was unchanged. A written consent was obtained from each subject and the project was accepted by the local Ethics Committee.

Study design

Subjects made one visit to the laboratory in the morning. After baseline assessment of lung resistance (R_L) and spirometry according to the criteria of the American Thoracic Society [5], subjects inhaled cold dry air for 3 min at the level of ventilation that had been

shown to cause a 20% change in forced expiratory volume in one second (FEV_1) during previous assessment. RL was continuously monitored for 3–4 min, at which time subjects were asked to take a fast vital capacity breath without holding it. In situations of induced bronchoconstriction, this manoeuvre has been shown to cause more bronchodilatation than a slow vital capacity breath [6, 7]. RL was again monitored continuously. After recovery (<1 min), the manoeuvre was repeated and RL was reassessed. The manoeuvre was then repeated a third time. After functional recovery to the baseline RL value obtained before hyperventilation, progressively doubling doses of methacholine from 0.03 mg·ml^{-1} were inhaled until the increase in RL was comparable to that obtained after hyperventilation. The same deep inspiratory manoeuvre was repeated three times with recovery as after hyperventilation.

Cold air inhalation test

This test was performed as described previously [8] using a freon air-conditioner which produces an adequate volume of cold (-20°C) dry air. Subjects listened to a tape-recording of breathing frequencies. During the test, a technician monitored tidal volume breathing, by asking subjects to breathe less deeply, as deeply, or more deeply, in order to obtain the desired level of ventilation.

Methacholine inhalation test

This test was carried out with a Wright nebulizer (output 0.14 ml·min^{-1}) at tidal volume breathing for 2 min using standardized methodology [9]. After normal physiologic saline (NPS) inhalation, progressively doubling doses of methacholine were administered until RL had increased to a level comparable to the increase obtained after hyperventilation.

Materials

Baseline FEV_1 and forced vital capacity (FVC) were measured on a Collins 9 *l* water spirometer (Collins Braintree, Mass.). RL was measured in a flow-displacement body plethysmograph. Flow at the mouth was measured with a Fleisch No.4 pneumotachograph connected to a Validyne (MP45 ±2 cmH$_2$O) pressure transducer. Pleural pressure was estimated by means of a 10 cm oesophageal balloon [10] connected to a Validyne (MP45 ±100 cmH$_2$O) differential pressure transducer *via* a 100 cm polyethylene catheter. The other side of the transducer was connected to an oral pressure tap to provide transpulmonary pressure. Transpulmonary pressure compensated for lung volume and buccal flow were continuously monitored on an oscilloscope and recorded on paper.

Analysis of results

RL was calculated from the paper recordings relating peak to peak changes in transpulmonary pressure and buccal flow as the ratio of transpulmonary pressure to flow at the mouth after electrical subtraction on the pressure signal of the signal proportional to the elastic component [11]. Baseline values of RL were obtained by averaging the results of eight consecutive breaths. After each deep inspiration, measurement means of two consecutive RL values obtained every 10 s were kept for analysis. The lowest value obtained after deep inspiration (<30 s in most cases) was kept for analysis. Percentage changes in RL after the manoeuvre were calculated using the following formula: ((RL pre-manoeuvre - lowest RL post-manoeuvre)/RL pre-manoeuvre) × 100. RL was estimated without any correction for the lung volume (functional residual capacity, FRC) which was not measured. We therefore assumed that changes in FRC after either hyperventilation or methacholine were similar.

For each methacholine concentration, the percentage change in RL was calculated using the following formula: % change = ((lowest value post-NPS - lowest value post-methacholine)/ lowest value post-NPS) × 100. Dose-response curves were drawn on a semilog scale, percentage change on the ordinate, and methacholine concentration on the abscissa. The concentration causing a 40% increase in RL (PC_{40}) was obtained from interpolation on the individual dose-response curves except for one subject (No. 3) for whom the changes reached 37%. PC_{40} was therefore extrapolated for this subject.

Reference values for spirometry were obtained from KNUDSON *et al.* [12]. Linear regression and paired t-tests were used in the statistical analysis when appropriate. A p value <0.05 was considered to be significant.

Results

The subjects' mean age was 51±10 (SD) yrs and their duration of asthma was 14±10 yrs. Six subjects had significant airway obstruction with an FEV_1 <80% pred and an FEV_1/FVC ratio <85% pred [12]. Mean baseline RL was 0.54±0.36 kPa·*l*$^{-1}$·s before the hyperventilation test and 0.53±0.31 kPa·*l*$^{-1}$·s before the methacholine test (t=0.02, p=1). All subjects had moderate to severe bronchial hyperresponsiveness [13] with a mean PC_{40} of 0.18 mg·ml^{-1} (range 0.04–0.9 mg·ml^{-1}). The mean percentage increases in RL were 55.6% (range 33.3–81.3%) after hyperventilation and 65.0% (range 36.8–104.3%) after methacholine inhalation. These figures are not significantly different (t=0.99, p=0.35). Baseline values of RL were not significantly different before each of the three consecutive deep inspiratory manoeuvres in the situations of hyperventilation- and methacholine-induced bronchoconstriction (mean values of 0.81, 0.82 and 0.85 kPa·*l*$^{-1}$·s for hyperventilation and 0.84, 0.85 and 0.84 kPa·*l*$^{-1}$·s for methacholine). Table 1 shows the individual changes in RL after each of the

Table 1. – Bronchomotor effects of deep inspiration on hyperventilation-induced and methacholine-induced bronchoconstriction

No.	Hyperventilation-induced bronchoconstriction						Methacholine-induced bronchoconstriction					
	1st manoeuvre		2nd manoeuvre		3rd manoeuvre		1st manoeuvre		2nd manoeuvre		3rd manoeuvre	
	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
1	0.87	0.97 (+12%)	1.02	0.88 (-14%)	1.10	0.97 (-13%)	0.96	0.93 (-3.1%)	1.00	0.97 (-3.0%)	0.92	0.93 (+1.0%)
2	0.91	0.64 (-30%)	0.75	0.58 (-23%)	0.8	0.48 (-40%)	0.87	0.55 (-36.8%)	0.83	0.45 (-45.8%)	0.80	0.51 (-36.3%)
3	1.19	1.16 (-2.5%)	1.41	1.13 (-19.9%)	1.4	1.24 (-11.4%)	1.04	0.93 (-10.6%)	1.04	1.02 (-1.9%)	1.14	0.98 (14.1%)
4	1.91	1.75 (-8.4%)	1.8	1.57 (12.8%)	2.01	1.61 (19.9%)	1.86	1.70 (-8.6%)	1.97	1.58 (-20.0%)	1.84	1.94 (+5.4%)
5	0.64	0.63 (-1.6%)	0.71	0.56 (-21.1%)	0.66	0.63 (-4.5%)	0.73	0.57 (-23.3%)	0.74	0.71 (-4.1%)	0.81	0.60 (25.9%)
6	0.35	0.34 (-2.9%)	0.38	0.36 (-5.3%)	0.36	0.36 (0%)	0.48	0.46 (-4.2%)	0.52	0.46 (-11.5%)	0.55	0.43 (-21.8%)
7	0.44	0.33 (-22.7%)	0.54	0.32 (-40.7%)	0.48	0.33 (-31.3%)	0.38	0.25 (-34.2%)	0.36	0.30 (-17.0%)	0.36	0.25 (-30.6%)
8	0.39	0.29 (-25.6%)	0.32	0.27 (-15.6%)	0.32	0.29 (-9.4%)	0.43	0.45 (+4.7%)	0.49	0.46 (-6.1%)	0.47	0.41 (-12.8%)
9	0.68	0.61 (-10.3%)	0.65	0.62 (-4.6%)	0.65	0.61 (-6.5%)	0.79	0.68 (-13.9%)	0.74	0.65 (-12.3%)	0.73	0.57 (-21.9%)
10	0.68	0.56 (-17.6%)	0.65	0.62 (-4.6%)	0.69	0.55 (-20.3%)	0.84	0.70 (-16.7%)	0.80	0.68 (-15.0%)	0.74	0.63 (-14.9%)
Mean SD		(-10.9%) (±12.8%)		(-16.1%) (±11.0%)		(-15.6%) (±12.5%)		(-14.7%) (±13.4%)		(-13.7%) (±12.9%)		(-17.2%) (±13.2%)

Values of R_L (kPa·l^{-1}·s) before (pre) and after (post) the 3 deep inspiratory manoeuvres separated by a recovery period (see text). The % change from the pre-manoeuvre value after inhaling to total lung capacity is shown in brackets. There were no statistical differences in the changes observed after hyperventilation and methacholine or between the effects after the three manoeuvres in each instance.

three manoeuvres following hyperventilation- and methacholine-induced bronchoconstriction. In general, no significant difference was demonstrated in the effect obtained after each of the three manoeuvres. Two subjects (Nos 2 and 7) almost consistently showed changes in R_L >20% after each manoeuvre after exposure to both stimuli. There were no significant differences between the effects of inspiratory manoeuvres after both stimuli (t=0.34, p=0.76). There was a satisfactory correlation between the mean bronchodilator effect of deep inspiration after both stimuli (r=0.80).

The bronchodilatation obtained after deep inspiration was significantly related to baseline airway calibre as assessed by FEV_1 (r=0.76 in the case of hyperventilation and r=0.81 for methacholine). However, we found no significant correlation between the bronchodilator effect of deep inspiratory manoeuvres and bronchial hyperresponsiveness (r=0.57 and 0.13 for hyperventilation and methacholine, respectively).

Discussion

Our study shows that the bronchodilatation that follows deep inspiration in a situation of induced bronchoconstriction is not significantly different with a pharmacological agent (methacholine) and a "natural stimulus" (hyperventilation of unconditioned air). So far, this phenomenon has been documented primarily following the inhalation of pharmacological agents [6, 14–18]. Two recent articles [1, 2] documented the same phenomenon after the inhalation of cold dry air, a stimulus that was also used in this study. However, direct comparison of the bronchodilator effect of deep inspiration on the bronchoconstriction induced by both stimuli had not previously been examined in the same asthmatic subjects.

The bronchodilatation that was observed in our study was minor as a rule, except in two subjects where it was almost consistently >20%. Considering that the within-individual coefficient of variation of R_L is at least 8% [19], spontaneous variability close to 20% can be expected. This can explain the variability of the effect of the inspiratory manoeuvres. Any change <20% is thus considered as minor. This phenomenon seems less common using hyperventilation as compared to pharmacological agents when it occurs more often, especially in those subjects with mild airway hyperresponsiveness. The magnitude of the bronchodilator effect was less than that found in previous studies using pharmacological agents. This can be explained by the fact that our subjects had more severe asthma as documented by their need for medication (all subjects required regular medication and six were on inhaled beclomethasone), baseline airway calibre (six had significant baseline bronchial obstruction) and their moderate to severe level of bronchial hyperresponsiveness. Subjects with significant bronchial hyperresponsiveness to hyperventilation of cold dry air generally have more pronounced hyperresponsiveness to pharmacological agents [20]. We found a significant

relationship between the magnitude of bronchodilatation and baseline airway calibre. This has also been shown in other studies [16, 18].

One interesting finding of our study, which has been documented by other groups [14, 21] using pharmacological agents but not hyperventilation, is that there was no tachyphylaxis in the bronchodilator effect when the manoeuvre was repeated on two consecutive occasions.

It has been shown that assessing bronchoconstriction by means of FEV_1 during challenges with pharmacological agents can result in false negative results (absence of or diminished changes in FEV_1) due to the bronchodilator effect of the deep inspiration which is required for FEV_1 [6, 16]. Hyperventilation of unconditioned air has been proposed for the assessment of bronchial hyperresponsiveness in clinical [19] and epidemiological surveys [22]. FEV_1 is also generally used to assess hyperresponsiveness. Results of this study which show that deep inspiration has a similar effect on bronchoconstriction induced by hyperventilation and pharmacological agents suggest that both types of stimuli can result in false negative results when subjects are asked to perform the FEV_1 manoeuvre. However, this phenomenon seems to be less common in the case of hyperventilation as only two subjects showed marked bronchodilatation after hyperventilation-induced bronchoconstriction. Moreover, this effect which might favour the use of manoeuvres not requiring a deep breath manoeuvre, is counterbalanced by the fact that functional tests which do not use maximum expiratory manoeuvres such as airway resistance or conductance and maximum flows in the lower half of forced vital capacity are less reproducible than those using FEV_1, thus resulting in greater overlap in the distinction between asthmatic and non-asthmatic populations [13, 23].

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Effets comparatifs des antécédents de volume pulmonaire sur la bronchoconstriction induite par l'hyperventilation et la methacholine chez des sujets asthmatiques. J.-L. Malo, J. L'Archevêque, A. Cartier.

RÉSUMÉ: Le but de notre étude est de déterminer si la bronchodilatation secondaire à une inspiration maximale peut être induite après inhalation d'un stimulus "naturel" (l'hyperventilation d'air froid sec) et si l'effet est comparable à celui noté après inhalation de méthacholine. Après l'évaluation de la résistance pulmonaire (RL) de base, 10 sujets asthmatiques ont respiré de l'air froid sec durant 3 minutes. La RL fut évaluée continuellement durant 3–4 minutes puis les sujets prirent une respiration maximale rapidement. Après récupération, la manoeuvre d'inspiration maximale fut répétée et la RL remesurée. La manoeuvre fut finalement effectuée une dernière fois. Après récupération fonctionnelle, des doses progressives de méthacholine furent inhalées jusqu'à ce que l'augmentation de la RL soit comparable à celle obtenue après l'hyperventilation (56±16% et 65±24%, respectivement, moyenne±SD, NS). La même inspiration profonde fut répétée trois fois avec récupération comme après l'hyperventilation d'air froid sec. Les changements maximaux de la RL ne furent pas significativement différents après chacune des trois manoeuvres selon les deux types de bronchospasme induit. La chute moyenne de la RL fut de 14.2±9.9% après l'hyperventilation et 16.4±10.5% après la méthacholine. Nous avons noté une corrélation satisfaisante (r=0.80, p<0.01) entre la bronchodilatation après une inspiration profonde pour les deux types de stimulus. Nous concluons que l'effet bronchodilatateur d'une inspiration maximale n'est pas différent dans une situation de bronchoconstriction induite par un agent pharmacologique (la méthacholine) ou un stimulus "naturel" (l'hyperventilation d'air non conditionné). Ces résultats suggèrent que l'évaluation de la réponse bronchoconstrictrice après l'hyperventilation avec des manoeuvres nécessitant la prise d'inspiration maximale (VEMS) peut altérer le tonus bronchique de la même manière que pour les agents pharmacologiques.
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