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Influence of the duration of inhalation of cold dry air on the resulting bronchoconstriction in asthmatic subjects

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ABSTRACT: Hyperventilation of cold dry air causes bronchoconstriction in asthmatic subjects and has been proposed as a test for assessing bronchial hyperresponsiveness. The influence of the duration of inhalation of unconditioned cold air has not been studied. We have investigated the question in 12 asthmatic subjects in a clinically stable state. Each subject underwent three inhalation tests at a maximum interval of two weeks. On each day, the duration of inhalation was different, being randomly 2, 3 or 4 min depending on the subject. Doubling doses of cold air produced by a freon conditioner were administered, increasing ventilation from 7.5 to 15, 30, 60 $l \cdot min^{-1}$ and maximum voluntary ventilation (MVV). Forced expiratory volume in one second (FEV_1) was assessed after each period of cold air inhalation. The test was stopped when the FEV_1 had decreased by 20% or more, or when MVV had been achieved. The dose of cold air expressed as the level of ventilation causing a 20% change in FEV_1 (PD_{20}) was interpolated from individual dose-response curves. Dose-response curves shifted to the left when the duration of ventilation was increased. PD_{20} was significantly lower after 3 min of ventilation than after 2 min (mean±SD PD_{20} of 41.7±1.4 $l \cdot min^{-1}$ compared with 53.3±1.2 $l \cdot min^{-1}$; p=0.002). There was a further fall in PD_{20} after 4 min of ventilation (PD_{20}=36.1±1.5 $l \cdot min^{-1}$) but the difference compared with the values obtained after 3 min was not significant (p=0.09), thus suggesting a plateau. These differences could not be accounted for by different levels of ventilation during the hyperventilation test. We conclude that the ideal duration of hyperventilation to obtain significant bronchoconstriction is 3 min.

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Hyperventilation of unconditioned air was first used to assess the mechanisms of exercise-induced asthma [1]. Since then, it has been proposed as a test for bronchial responsiveness in clinical and epidemiological studies [2, 3]. Dose-response curves by increasing levels of ventilation have been proposed, and the duration of hyperventilation at each level has been set at 3 or 4 min [4, 5]. However, the ideal duration of ventilation has not been evaluated. There are reasons to suspect that increasing the duration of ventilation will result in a greater burden on the bronchial tree as it conditions the air [6], which would cause greater bronchoconstriction. Information on the influence of the duration of hyperventilation would be useful in standardizing the test for clinical use. Furthermore, it would be relevant to know if increasing the duration might result in diminishing the level of ventilation that could be reached at the end of each step.

In this study, we obtained dose-response curves to hyperventilation of cold dry air for progressive durations of 2, 3 and 4 min in 12 asthmatic subjects.

Material and methods

Subjects

Twelve adult subjects who satisfied the criteria for a diagnosis of asthma [7] were included in the study. All were in a clinically stable state as judged by clinical criteria (absence of nocturnal awakenings due to asthma, no recent need for extra medication) and functional criteria (forced expiratory volume in one second (FEV_1) varying by ≤10% from one visit to the next). Atopic subjects had not recently experienced antigenic contact (pollens, animal danders) except for house dust and no subject had suffered a recent (≤2 months) respiratory infection. Bronchodilators were stopped in 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 [8]. Use of inhaled beclomethasone was unchanged. A written consent was

Table 1. – Baseline anthropometric, clinical and functional results

No.	Sex	Age	Height	Duration of asthma	Atopy*	Medication	FEV_1		FEV_1/FVC		PD_{20}
		yrs	cm	yrs			*l*	%pred	%	%pred	$l \cdot min^{-1}$
1	F	52	163	1	-	B2; be 600	1.8	70	80	90	33
2	F	16	180	4	-	B2	3.6	99	83	95	55
3	F	58	160	9	-	B2; T; be 200	1.7	71	76	94	32
4	F	47	182	12	-	B2; T; be 200	2.8	83	76	94	44
5	M	45	168	6	-	B2; T; be 300	4.0	118	75	92	74
6	F	40	153	8	-	B2	2.9	115	85	100	66
7	F	20	159	6	-	B2	3.5	114	88	102	55
8	M	48	168	15	+	B2; be 400	2.6	80	72	88	40
9	F	52	157	3	+	B2; T	2.6	108	76	92	39
10	F	25	163	20	+	B2; T; be 400	2.3	74	71	84	33
11	F	55	157	43	-	B2; T; be 800	1.5	64	77	94	34
12	F	57	153	22	-	B2; T; be 400	1.5	71	69	84	23
Mean		43	164	12			2.6	89	72	92	42[1]
SD		15	10	12			0.8	20	20	6	1.4

Atopy*: + if the subject had at least one positive skin reaction to 15 common inhalant allergens; B2: inhaled $beta_2$-adrenergic agent; T: oral sustained theophylline derivative; be: inhaled beclomethasone (daily dose); [1]: geometric means and SD of the PD_{20} value obtained on the occasion of the 3 min hyperventilation test; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

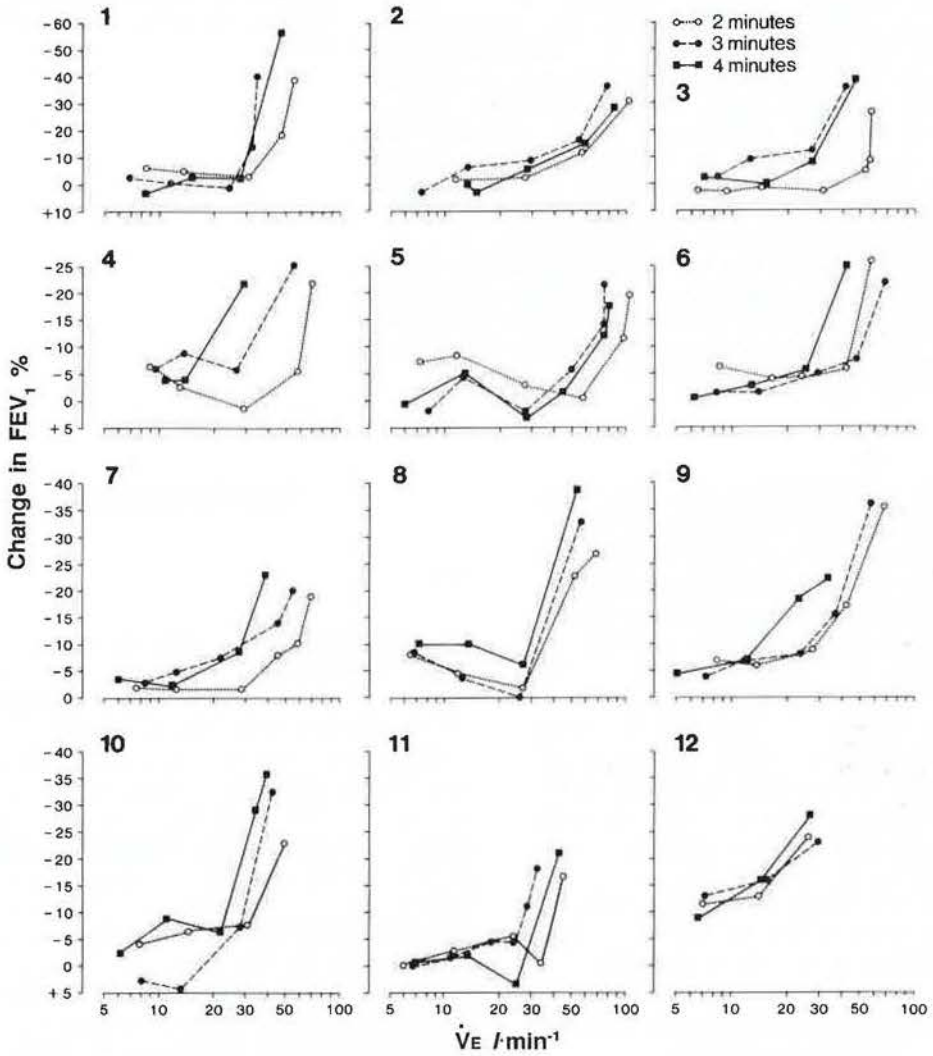

Fig. 1. – Individual dose-response curves for the 12 subjects (nos corresponding to those in table 1) on a semilogarithmic scale. FEV_1: forced expiratory volume in one second; $\dot{V}_E$: minute ventilation. Duration of ventilation is shown.

obtained from each subject and the project was accepted by the local ethical committee.

Study design

Subjects came on three different days at a maximum interval of two weeks. After assessing baseline spirometry, including FEV_1 and forced vital capacity (FVC) [9] with a Collins 9 *l* water spirometer (W.E. Collins, Braintree, Mass), cold dry air inhalation tests were performed as previously described [10], increasing levels of ventilation from 7.5 to 15, 30, 60 $l \cdot min^{-1}$ and maximal voluntary ventilation (MVV). FEV_1 was assessed at each level. The tests were stopped when FEV_1 had dropped by 20% or more. On each study day, the duration of ventilation varied and its sequence was randomly assigned: 2, 3 and 4 min; 2, 4 and 3 min; 3, 2 and 4 min; 3, 4 and 2 min; 4, 3 and 2 min; and finally, 4, 2 and 3 min. There were two subjects for each randomization.

Analysis of results

Reference values for FEV_1 and FEV_1/FVC were obtained from KNUDSON *et al.* [11]. Dose-response curves to cold air inhalation were drawn on a non-cumulative semilogarithmic scale using minute ventilation ($\dot{V}E$) on the abscissa. It has been shown that $\dot{V}E$ can be used instead of respiratory heat exchange as the two yield similar results [10]. The doses of cold air causing a 20% fall in FEV_1 were interpolated from the dose-response curves. Student's paired t-test with the Bonferroni correction [12], with a significance level of alpha/3 (alpha/number of comparisons) or 0.05/3 (0.0167) was used to compare the provocative dose causing a 20% fall in FEV_1 (PD_{20}) results. Analysis of variance with the Newman-Keuls contrast test, was used to compare levels of ventilation at each minute.

Results

Table 1 shows the baseline anthropometric, clinical and physiological results. The majority (9/12) of subjects were non-atopic. Seven subjects demonstrated significant airway obstruction (FEV_1 ≤80% pred and FEV_1/FVC ≤95% pred) [11].

Figure 1 shows the individual dose-response curves for the 12 subjects according to duration of ventilation. In 5 of the 12 subjects (nos 4 and 7–10), there was a parallel shift of the dose-response curve when the duration of ventilation was increased from 2 to 3 to 4 min. In 5 other subjects (nos 1–3, 5 and 11) this was only shown by increasing the duration from 2 to 3 min, without further significant shift after ventilating for 4 min. PD_{20} values are shown in table 2. Mean PD_{20} differed by more than 10 $l \cdot min^{-1}$ (20–25% change) when the duration of ventilation was increased from 2 to 3 min. PD_{20} was lower after ventilating for 3 min in every instance with two exceptions (nos 6 and 12). There were further changes in PD_{20} after 4 min as compared with after 3 min, but the mean difference was only around 5 $l \cdot min^{-1}$ (10–15% change) and was not statistically significant. PD_{20} was lower in 8 of the 12 subjects when the duration of ventilation was increased from 3 to 4 min.

Table 2. – PD_{20} values ($l \cdot min^{-1}$) according to duration of ventilation

No.	Duration of ventilation		
	2 min	3 min	4 min
1	48	33	32
2	78	55	68
3	55	32	34
4	67	44	27
5	103	74	83
6	52	66	38
7	68	55	38
8	48	40	35
9	46	39	27
10	45	33	29
11	48	34	42
12	22	23	18
Mean¶	53.3	41.7	36.1
SD	1.2	1.4	1.5
	t_1=3.92 p=0.002	t_2=1.88 p=0.09	
		t_3=5.93 p=0.0001	

t_1, t_2 and t_3: the t results of comparing 2 min and 3 min, 3 min and 4 min, and 2 min and 4 min, respectively; ¶: geometric mean and SD; PD_{20}: provocative dose producing 20% fall in forced expiratory volume in one second.

Table 3. – Levels of ventilation at each minute

Expected level	30 $l \cdot min^{-1}$				60 $l \cdot min^{-1}$			
Level obtained	1 min n=36	2 min n=36	3 min n=24	4 min n=12	1 min n=33	2 min n=33	3 min n=22	4 min n=11
Mean	25.2	25.7	24.8	25.0	39.9	43.1	43.1	43.2
SD	±3.0	±3.4	±3.4	±2.7	±8.3	±8.3	±8.3	±7.4
ANOVA	F=0.3, p=0.85				F=5.74, p=0.003 (significant contrasts: 1 min<2 min, 1 min<3 min, 1 min<4 min, p<0.05)			

The number of assessments for each minute of ventilation is given (n value); contrasts were made using the Newman-Keuls test in the case of the significant ANOVA (60 $l \cdot min^{-1}$). ANOVA: analysis of variance.

As shown in table 3, the level of ventilation obtained was slightly lower than expected. The level of ventilation actually reached at each minute for the expected levels of ventilation of 30 $l \cdot min^{-1}$ was not significantly different at each interval between 1 and 4 min (Table 3). The actual level of ventilation was significantly lower in the first minute for the expected 60 $l \cdot min^{-1}$ level of ventilation but increased and remained stable thereafter. Time needed to complete the test (excluding the time requested for ventilation) was not significantly different (19.2±5.4 min for the 2 min test, 19.3±1.0 min for the 3 min test and 17.5±4.2 min for the 4 min test).

Discussion

Hyperventilation of unconditioned air has been proposed as a test for assessing bronchial responsiveness. In previous studies, the duration of ventilation has been set at 3 [4, 10] or 4 [5] min. However, to the best of our knowledge, no information is available on the ideal duration of ventilation to achieve bronchoconstriction. This study shows that increasing the duration of ventilation from 2 to 3 min increases response in terms of a more significant fall in FEV_1. The dose-response curve shifted in 10 of the 12 subjects. Such changes from a mean PD_{20} of 53.3 to 41.7 $l \cdot min^{-1}$ (difference of 0.24 on a $\log_e$ scale) are approximately half of the within-day within-subject reproducibility of the test as assessed by the 95% confidence interval (±0.43 on a $\log_e$ scale). Ventilating for 4 min resulted in a further increase in response in 8 of the 12 subjects but the increase was physiologically minimal (10–15%) and statistically not significant. Assoufi *et al.* [13] found that the bronchoconstrictor response was equivalent by asking subjects to ventilate for 3 and 5 min. However, this applied for a single level of ventilation and not for a dose-response curve as in the present study.

Although it could only have been proven by increasing the duration of ventilation to 5 or more min, we suspect the presence of a plateau of response to hyperventilation. A plateau of response was originally found using pharmacological agents [14, 15]. More recently, a plateau was documented in asthmatic children by Zach and Polgar [16], and in young adults by Smith and Anderson [17]. These authors had subjects ventilate to 70–75% of their predicted MVV for 10 min; response was assessed after each minute of hyperventilation. Dose-response curves reached a plateau after 6–8 min of ventilation. Several explanations for this plateau were proposed by these authors. Hyperventilation with its effect on airway tone may have caused bronchodilatation when the subjects were asked to ventilate at levels close to total lung capacity [18]. After a while, the bronchoconstrictive effect of breathing unconditioned air may have been "balanced" by the bronchodilator effect of taking deep breaths. Furthermore, the obstructive reaction may be limited by intrinsic bronchodilator mechanisms through the release of bronchodilatating substances. It is also suspected that there are some limiting factors in the capacity of receptors in the airway mucosa to be triggered by unconditioned air. Indeed, dose-response relationships to pharmacological agents generally display a sigmoid curve as fully reviewed elsewhere [19]. Also, this plateau can be due to the decreasing potential for water loss to increase osmolarity in the more peripheral regions of the tracheobronchial tree [17]. Finally, onset of tachyphylaxis might have occurred as subjects were required to ventilate continuously for 10 min. Tachyphylaxis to repeated hyperventilation tests has indeed been described by several authors [20–22].

Increasing the number of points on the dose-response curves by augmenting the level of ventilation by 5 $l \cdot min^{-1}$ at each step as in a previous study [23] would have offered a better characterization of the dose-response curve as up to 13 points could have been included. However, this would have been difficult as asking subjects to hyperventilate for 4 min proved uncomfortable for the five steps requested in the present study.

Since increasing the duration of ventilation in the study we conducted did not result in any significant diminution of ventilation, this cannot be proposed as an explanation for the lack of significantly greater bronchoconstriction after 4 min. The absence of reduction in the level of ventilation between 2 and 4 min duration is another relevant finding of our study. Indeed, the level of ventilation, more than the dryness or temperature of the inspired air, is the principal determinant of the magnitude of bronchoconstriction induced by cold dry air [1].

We have shown that the target levels of ventilation at 30 $l \cdot min^{-1}$ and, even more so, at 60 $l \cdot min^{-1}$ were not obtained. This was also shown in a previous work [23]. There is a progressive limit in the ventilatory capacity, principally brought on by bronchoconstriction.

Although hyperventilation of cold dry air is less sensitive than are pharmacological agents in testing for bronchial hyperresponsiveness [24], there are several advantages which warrant efforts to standardize the test. In epidemiological studies, they may be more acceptable than inhalation of pharmacological agents from an ethical point of view as cold dry air is a natural stimulus [3]. Furthermore, the effect of drugs on bronchial responsiveness might be better assessed using a natural rather than a pharmacological stimulus [25, 26]. Different aspects of the hyperventilation test have been examined by Assoufi *et al.* [13]: varying the time intervals between each inhalation and the pattern of ventilation (different rates but similar levels of ventilation) do not affect the result of the test; using subfreezing air (-15°C) yields more pronounced bronchoconstriction than dry room air (21°C). Other relevant points of the methodology by obtaining dose-response curves have been assessed previously: within-day and between-day reproducibility of the test [9] and cumulative aspects of the dose-response curve [27]. Kinetics of recovery from bronchoconstriction [28] which assessed the best timing for measuring the response have also been evaluated. From the results presented in this study, we recommend that dose-response curves should be obtained by increasing ventilation during periods of 3 min.

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References

1. Deal EC, McFadden ER, Ingram RH, Strauss RH, Jaeger JJ. – Role of respiratory heat exchange in production of exercise-induced asthma. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1979, 46, 467–475.
2. Chandler DE, McFadden ER, Ingram RH, Breslin F, Jaeger JJ. – Airway responsiveness to cold air and hyperpnea in normal subjects and in those with hay fever and asthma. *Am Rev Respir Dis*, 1980, 121, 621–628.
3. Weiss AT, Tager IB, Weiss JW, Munoz A, Speizer FE, Ingram RH. – Airways responsiveness in a population sample of adults and children. *Am Rev Respir Dis*, 1984, 129, 898–902.
4. O'Byrne PM, Ryan G, Morris M, *et al.* – Asthma induced by cold air and its relation to nonspecific bronchial responsiveness to methacholine. *Am Rev Respir Dis*, 1982, 125, 281–285.
5. Weiss JW, Rossing TH, McFadden ER, Ingram RH. – Relationship between bronchial responsiveness to hyperventilation with cold air and methacholine in asthma. *J Allergy Clin Immunol*, 1983, 72, 140–144.
6. McFadden ER, Ingram RH. – Thermal factors in respiratory mechanics. *In:* Handbook of Physiology. Vol III. A.P. Fishman, P.T. Macklem, J. Mead and S.R. Geiger eds, Williams and Wilkins, Baltimore, 1986, pp. 703–709.
7. American Thoracic Society. – Chronic bronchitis, asthma, and pulmonary emphysema. *Am Rev Respir Dis*, 1962, 85, 762–768.
8. Chai H, Farr RS, Froehlich LA, *et al.* – Standardization of bronchial inhalation challenge procedures. *J Allergy Clin Immunol*, 1975, 56, 323–327.
9. ATS statement. – Standardization of spirometry. 1987 Update. *Am Rev Respir Dis*, 1987, 136, 1285–1298.
10. Tessier P, Cartier A, L'Archevêque J, Ghezzo H, Martin RR, Malo JL. – Within- and between-day reproducibility of isocapnic cold air challenges in subjects with asthma. *J Allergy Clin Immunol*, 1986, 78, 379–387.
11. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. – Changes in normal maximal expiratory flow-volume curve with growth and ageing. *Am Rev Respir Dis*, 1983, 127, 725–734.
12. Godfrey K. – Comparing the means of several groups. *N Engl J Med*, 1985, 313, 1450–1456.
13. Assoufi BK, Dally MB, Newman-Taylor AJ, Denison DM. – Cold air test: a simplified standard method for airway reactivity. *Bull Eur Physiopathol Respir*, 1986, 22, 349–357.
14. Michoud MC, Lelorier J, Amyot R. – Factors modulating the interindividual variability in airway responsiveness to histamine. The influence of H1 and H2 receptors. *Bull Eur Physiopathol Respir*, 1981, 17, 807–821.
15. Woolcock AJ, Salome CM, Yan K. – The shape of the dose-response curve to histamine in asthmatic and normal subjects. *Am Rev Respir Dis*, 1984, 130, 71–75.
16. Zach MS, Polgar G. – Cold air challenge of airway hyperreactivity in children: dose-response interrelation with a reaction plateau. *J Allergy Clin Immunol*, 1987, 80, 9–17.
17. Smith CM, Anderson SD. – A comparison between the airway response to isocapnic hyperventilation and hypertonic saline in subjects with asthma. *Eur Respir J*, 1989, 2, 36–43.
18. Lim TK, Pride NB, Ingram RH. – Effects of volume history during spontaneous and acutely induced air-flow obstruction in asthma. *Am Rev Respir Dis*, 1987, 135, 591–596.
19. Tallarida RJ, Jacob LS. – *In:* The dose-response relation in pharmacology. Springer-Verlag, New York, 1979.
20. Bar-Yishay E, Ben-Dov I, Godfrey S. – Refractory period after hyperventilation-induced asthma. *Am Rev Respir Dis*, 1983, 127, 572–574.
21. Rakotosihanaka F, Melaman F, d'Athis P, Florentin D, Dessanges JF, Lockhart A. – Refractoriness after hyperventilation-induced asthma. *Bull Eur Physiopathol Respir*, 1986, 22, 581–587.
22. Soto ME, Schnall R, Landau LI. – Refractoriness to bronchoconstriction following hyperventilation with cold dry air. *Pediatr Pulmonol*, 1985, 1, 80–84.
23. Tessier P, Ghezzo H, L'Archevêque J, Cartier A, Malo JL. – Shape of the dose-response curve to cold air inhalation in normal and asthmatic subjects. *Am Rev Respir Dis*, 1987, 136, 1418–1423.
24. Desjardins A, De Luca S, Cartier A, L'Archevêque J, Ghezzo H, Malo JL. – Nonspecific bronchial hyperresponsiveness to inhaled histamine and hyperventilation of cold dry air in subjects with respiratory symptoms of uncertain etiology. *Am Rev Respir Dis*, 1988, 137, 1020–1025.
25. O'Byrne PM, Morris M, Roberts R, Hargreave FE. – Inhibition of the bronchial response to the respiratory heat exchange by increasing doses of terbutaline sulphate. *Thorax*, 1982, 37, 913–917.
26. Merland N, Cartier A, L'Archevêque J, Ghezzo H, Malo JL. – Theophylline minimally inhibits bronchoconstriction induced by dry cold air inhalation in asthmatic subjects. *Am Rev Respir Dis*, 1988, 137, 1304–1308.
27. Malo JL, Cartier A, L'Archevêque J, Ghezzo H, Martin RR. – Cold air inhalation has a cumulative bronchospastic effect when inhaled in consecutive doses for progressively increasing degrees of ventilation. *Am Rev Respir Dis*, 1986, 134, 990–993.
28. Malo JL, Cartier A, L'Archevêque J, Ghezzo H, Martin RR. – Kinetics of the recovery from bronchial obstruction due to hyperventilation of cold air in asthmatic subjects. *Eur Respir J*, 1988, 1, 384–388.

Influence de la durée d'inhalation d'air froid et sec sur la bronchoconstriction chez les sujets asthmatiques. N. Caire, A. Cartier, H. Ghezzo, J.L. Malo.

RÉSUMÉ: L'hyperventilation d'air froid sec cause une bronchoconstriction chez les asthmatiques. On a proposé ce test pour évaluer l'hyperexcitabilité bronchique non-allergénique. L'influence de la durée de l'inhalation d'air mal conditionné n'a pas été évaluée. Nous avons étudié ce problème chez 12 sujets asthmatiques en état clinique stable. Chaque sujet a subit 3 tests d'hyperventilation à un intervalle maximum de 2 semaines. Chaque jour, la durée de l'inhalation était variable, soit 2, 3 ou 4 minutes, au hasard. Nous avons demandé au sujet de d'inhaler des doses progressivement doublées d'air froid soit 7.5, 15, 30, 60 $l \cdot min^{-1}$ puis à ventilation maximale volontaire. La réponse bronchoconstrictrice fut évaluée par le VEMS après chaque période de ventilation. Nous avons arrêté le test lorsqu'une chute de 20% ou plus du VEMS survenait ou quand la ventilation maximale volontaire était atteinte. La dose d'air froid sec exprimée en tant que niveau de ventilation causant une chute de 20% du VEMS (PD_{20}) fut intrapolée de chacune des courbes dose-réponse. Les courbes dose-réponse se sont déplacées vers la gauche lorsque la durée de ventilation augmentait. La PD_{20} était significativement plus basse après 3 minutes de ventilation par comparaison avec 2 minutes (moyennes et écarts types de PD_{20}=41.7±1.4 $l \cdot min^{-1}$ et 55.3±1.2 $l \cdot min$ respectivement, p=0.002). Nous avons noté une chute supplémentaire de la PD_{20} après 4 minutes de ventilation (PD_{20}=36.1±1.5 $l \cdot min^{-1}$) mais cette différence n'était pas significative (p=0.09) par comparaison avec la période de 3 minutes, ce qui suggère un plateau. Ces différences n'ont pu être expliquées par des différences des niveaux de ventilation lors du test. Nous concluons que la période idéale de ventilation pour obtenir une bronchoconstriction significative est de 3 minutes.

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