

Kinetics of the recovery from bronchial obstruction due to hyperventilation of cold air in asthmatic subjects

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ABSTRACT: The timecourse of recovery from bronchial obstruction due to inhaled cold air was studied in eight adult asthmatic subjects. On the first visit, bronchial responsiveness to inhaled histamine was assessed. On the other two visits, after assessment of baseline lung resistance (R_L) and spirometry, dry cold (-20°C) air was inhaled for three minutes. R_L was monitored continuously until its return to baseline $\pm 20\%$. The baseline concentration of histamine causing a 20% fall in FEV_1 (PC_{20}) varied from 0.03 to 5.9 $\text{mg}\cdot\text{ml}^{-1}$. The mean maximum increase in R_L was 2-fold (2.03 ± 0.41) and was reached 2-11 min after the challenge. R_L values were linearly correlated to time (r^2 values > 0.80 in 14/16 instances). The two slopes of recovery were not significantly different. Slopes of recovery and total time of recovery (14-55 min) varied greatly between subjects. No relationship was found between baseline airway calibre, bronchial hyperresponsiveness and maximal increase in baseline R_L on the one hand and the slopes of recovery on the other.

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The time-course of recovery from bronchial obstruction due to exercise has been described in asthmatic subjects. The response is maximal five to seven minutes after the end of exercise [1] with progressive recovery in the first hour [2]. Late bronchospastic reactions following exercise have been described occasionally, mainly in children [2, 3]. Bronchial obstruction induced by isocapnic hyperventilation of cold air has initially been proposed as a means of explaining the mechanisms of exercise-induced asthma [4, 5]. More recently, this test has been used for the clinical assessment of bronchial hyperresponsiveness [6-8]. However, kinetics of the recovery from hyperventilation-induced bronchial obstruction have not been studied. Proper standardization of this test for clinical use requires information on the best timing of assessment of airway calibre after application of the stimulus.

We characterized the kinetics of recovery from bronchial obstruction due to cold air in eight asthmatic subjects and assessed its reproducibility.

Material and methods

Subjects

The asthmatic subjects included in this study satisfied the criteria of the American Thoracic Society for asthma [9]. Every subject was in a clinically steady state according to clinical (absence of nocturnal awakenings due to asthma, minimal requirement for bronchodilator medication) and functional (baseline forced expiratory volume in one second (FEV_1) within $\pm 10\%$ between the three

study days) criteria. They had not reported airway infection and had not been exposed to relevant antigens (except for house dust) in the previous two months. They were required to stop their medication according to the proposals made by a special committee of the American Academy of Allergy [10], *i.e.* 8 h for inhaled beta-2 adrenergic agents and 48 h for sustained-release theophylline preparations. Inhaled beclomethasone was not interrupted. A written consent to participate in the study was obtained from each subject and the project accepted by the Hospital's ethics committee.

Study design

Subjects came on three different days within the same week for two similar cold air and histamine inhalation tests which were carried out without randomization.

Procedure

Cold air inhalation test

Baseline lung resistance (R_L), FEV_1 and forced vital capacity (FVC) were obtained first. FEV_1 and FVC, (from which forced mid-expiratory flow ($FEF_{25-75\%}$) was derived), were performed according to the criteria of the American Thoracic Society [11]. The cold air challenge was carried out as follows: an Air Jet Breathing Device (FTS System, Stoneridge, New York) allowed production of adequate volumes of dry air which could be conditioned to temperatures varying from -30 to $+40^\circ\text{C}$. The supply of dry air was provided by compressed air at 965 kPa. Cold

air was directed to the subject through a Hans Rudolph valve No. 2700 (Hans Rudolph, Kansas City, Miss), the extra air being evacuated in room air. The mouth-port of the valve was partitioned by a plexiglass wall in order to avoid contamination of the cold inspired air and the conditioned expired air. The expired air was first directed to a damping device. This damping device was a plastic box of approximately 28 l in which plastic walls slowed the mixing of air from the inner to the outer parts. The temperature of the expired air was thus kept constant, making the reading of flow by the pneumotachograph (Fleisch no. 3), through which the expired air was subsequently directed accurate. The recorded expiratory flow was electrically integrated per unit of time to provide minute-ventilation. Temperatures of the inspired ($-20 \pm 5^\circ\text{C}$ of maximum variation) and expired air were measured with probes which were positioned at a distance of 1 cm from the inspiratory side of the valve and at 1 cm from the mouth on the expiratory side of the valve. Rapidly responding (3 msec per $^\circ\text{C}$) thermocouples (Extech, Boston, Mass) allowed the assessment of inspired and expired temperatures which were continuously recorded on paper. A small volume of expired air was sampled continuously and provided measurement of expired CO_2 . A mixture of CO_2 (10%) and compressed air (90%) was added if needed in order to keep the expired CO_2 constant. Minute ventilation, respiratory frequency, tidal volume, expired CO_2 , and inspired and expired temperatures were continuously recorded on paper throughout the cold air inhalation.

Subjects were seated and inspired cold air at a level which was sufficient to cause significant bronchial obstruction. Subjects heard a taped recording of breathing noise frequencies (15 or 30 breaths $\cdot\text{min}^{-1}$). Tidal volume was set by continuously examining tidal volume recording and instructing the subject to breathe less, more, or as deeply. The level of minute ventilation was set for each subject in order to obtain significant bronchial obstruction. This had been determined by a previous cold air test for which increasing levels of minute ventilation were used.

After the inhalation of cold air for 3 min, the subject was immediately asked to sit in a flow displacement body plethysmograph to record lung resistance (RL). RL was used to monitor airway calibre as it is independent of the volume history. The interval between the end of cold air inhalation and the first measurement of RL was 1–2 min. RL was calculated according to the technique of MEAD and WHITTENBERGER [12]. Flow at the mouth was measured with a no. 4 pneumotachograph (Fleisch, Lausanne, Switzerland) connected to a Validyne MP 45 \pm 2 cmH_2O pressure transducer (Validyne Co., Northridge, CA). Pleural pressure was estimated by means of a 10 cm oesophageal balloon [13] connected to a Validyne MP 45 \pm 100 cmH_2O 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 lung volume

and buccal flow were continuously monitored on an oscilloscope and recorded on paper. The average RL was calculated from the paper recording by relating peak to peak changes in buccal flow and transpulmonary pressure-compensated lung volume from ten consecutive breaths after eliminating the highest and lowest values. Average values for RL were most often obtained every minute until it returned to baseline $\pm 20\%$. A Collins 9 l water spirometer (Warren E. Collins, Braintree, MA) was used to assess baseline spirometry in every subject.

Histamine inhalation test

This test was performed according to the method of COCKCROFT *et al.* [14] with a Wright nebulizer (output=0.14 $\text{ml}\cdot\text{min}^{-1}$; (Acrosol Products, London, England) at tidal volume breathing for 2 min.

Analysis of results

Curves relating RL (on the ordinate) to the time of the maximum response (on the abscissa) were fitted using a linear model. Correlation coefficients were obtained by the least-squares method. The two curves obtained for each subject were tested by an analysis of covariance (ancova) in order to find out whether they were significantly separated and had significantly different slopes. Paired t-test was used to compare minute ventilation and respiratory heat exchange (RHE) or, more precisely, energy losses, obtained on the two days of cold air challenges.

RHE (energy losses) were calculated from the equation of HOUDAS and COLIN [15] as validated by DEAL and co-workers [4, 5]. Reference values for FEV_1 , FEV_1/FVC and $\text{FEF}_{25-75\%}$ were obtained from KNUDSON *et al.* [16]. The concentration of histamine provocation causing a 20% fall in FEV_1 (PC_{20}) was obtained by interpolation on the dose-response curve drawn on a non-cumulative semi-logarithmic scale.

Logarithmic transformation of PC_{20} was used for the statistical analysis. Level of statistical significance was set at $p < 0.05$.

Results

Table 1 lists the baseline anthropometric, clinical and functional results of the eight asthmatic subjects. Five subjects showed significant airway obstruction as their FEV_1 was $< 80\%$ predicted. Mild to severe bronchial hyperresponsiveness to histamine was demonstrated in every subject.

The levels of minute ventilation and RHE, obtained for each subject on the two challenge days and shown in table 2, were not significantly different ($t=0.06$ and 0.04 respectively). The individual recovery curves of RL as a function of time are shown in figure 1. The mean maximum increase in RL was 2.03 times (range=1.55–2.87) the baseline value. Significant bronchial obstruction was noticed early after the challenge (1–2 min). Maximal bronchial obstruction was reached before the fifth minute of recording in all but one subject (no. 1)

Table 1. - Baseline anthropometric, clinical and functional results

n	Sex	Age yr	Height cm	Atopy*	Duration of asthma yr	Medication†	FEV ₁ l	FEV ₁ %pred	FEF _{25-75%} l·sec ⁻¹	FEF _{25-75%} %pred	PC ₂₀ mg·ml ⁻¹
1	M	65	172	+	35	B2; B	1.44	47.7	0.67	21.7	0.22
2	F	57	152	+	16	B2; B	1.50	70.1	0.71	29.7	0.22
3	F	62	163	-	5	B2; B	2.32	96.3	1.21	47.1	0.74
4	F	37	152	-	5	B2	3.15	125.0	3.65	121.3	5.9
5	F	22	170	+	7	B2	2.01	58.9	1.01	25.2	0.95
6	M	43	170	-	4	B2; T	2.84	80.4	1.11	29.5	0.50
7	F	54	152	-	21	B2; T; B	1.73	79.0	0.79	31.7	0.60
8	M	45	180	-	9	B2	2.46	59.4	1.32	30.9	0.03
MEAN:		48.1	163.9		12.8		2.18	77.1	1.31	42.1	0.45‡
SD:		14.3	10.9		10.8		0.62	24.6	0.98	32.8	4.51

*: at least one positive immediate skin reaction to a battery of 15 common inhaled allergens; †: B2=inhaled beta-2 adrenergic agent; B=inhaled beclomethasone; T=theophylline derivatives; ‡: geometric mean and SD.

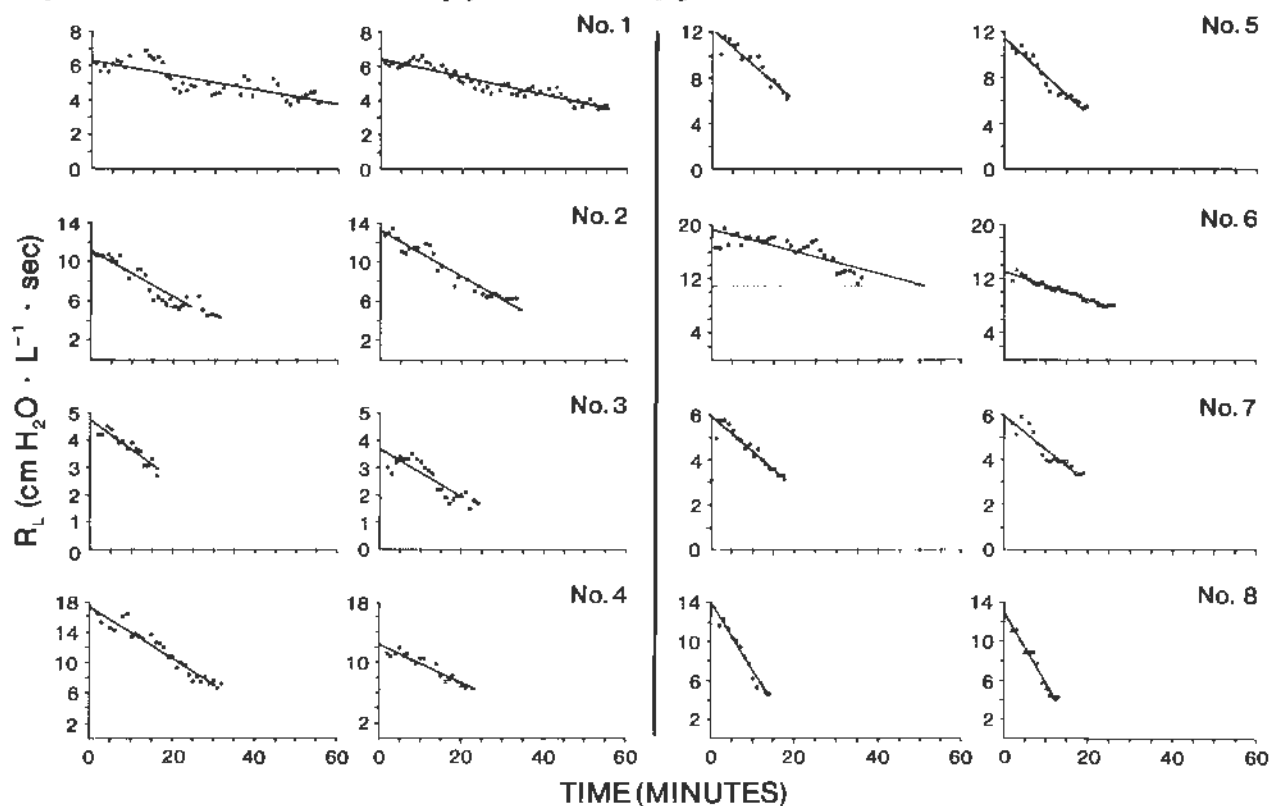


Fig. 1. - Curves relating lung resistance (R_L) and time. Each subject had two assessments. Subjects' numbers are the same as in tables I and 2. The horizontal dotted lines represent baseline values of R_L .

for whom it took 11 and 12 min. For each curve, the data (r^2 value for the linear fit, number of points (n), slope) derived from the analysis are given in table 2. The r^2 value was >0.80 in 14/16 instances. Results of the ancova of the two lines for each subject showed that the lines were highly significantly separate (i.e. the Y intercepts were

different) except for subjects nos 1 and 7. This means that, for the latter two subjects, highly reproducible increases in R_L were obtained on the two occasions, whereas, this increase differed for the other subjects. The slopes of recovery were not significantly different except for subject no. 4 for whom the difference just reached statistical

Table 2. - Characteristics of cold air challenges and statistical analysis of the curves

n	Challenge no.	Minute ventilation $l \cdot \text{min}^{-1}$	RHE Watt	r^2	n	slope $\text{cm H}_2\text{O} \cdot \text{s} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$	Ancova*			
							Between lines F	p	Parallelism F	p
1	1	37.8	90.6	0.63	46	-0.041	5.56	0.02	1.25	0.27
	2	38.2	89.3	0.89	53	-0.052				
2	1	27.0	57.9	0.89	29	-0.236	89.5	<0.001	~0	0.99
	2	29.3	62.1	0.93	29	-0.236				
3	1	42.4	91.3	0.85	16	-0.107	56.7	<0.001	0.72	0.40
	2	55.3	124.1	0.77	24	-0.087				
4	1	64.5	131.8	0.93	29	-0.340	224.4	<0.001	4.21	0.05
	2	66.0	139.5	0.88	19	-0.254				
5	1	60.8	126.2	0.88	16	-0.310	29.0	<0.001	0.36	0.56
	2	53.5	113.7	0.94	19	-0.326				
6	1	73.7	150.6	0.66	33	-0.162	868.0	<0.001	0.55	0.46
	2	58.9	121.3	0.95	26	-0.206				
7	1	57.0	120.6	0.90	18	-0.158	0.55	0.46	2.14	0.16
	2	49.2	104.6	0.86	18	-0.147				
8	1	55.0	118.5	0.96	14	-0.697	24.9	<0.001	0.25	0.62
	2	56.4	125.5	0.95	13	-0.723				

r^2 = squared coefficient of correlation; n = number of points; * Analysis of covariance: the between lines comparison indicates if the lines are significantly separate; the parallelism comparison shows if the lines have significantly different slopes.

significance.

We found no statistically significant correlation ($r = -0.09$, $r = -0.51$ and $r = -0.49$ respectively) between baseline R_L , the increase in R_L after the inhalation of cold air and baseline PC_{20} on one hand and the slopes of recovery on the other.

Discussion

Hyperventilation of cold air has initially been used as a stimulus to explain the mechanism of exercise-induced asthma [4, 5]. Some arguments reviewed extensively by LOCKHART *et al.* [17] may suggest that both stimuli are similar and act through a common pathway. Firstly, maximal bronchial obstruction after exercise is generally obtained five to seven minutes after the end of exercise with progressive recovery thereafter in the first hour [1, 2]. Detailed information on the kinetics of bronchial obstruction due to exercise is unavailable, as a sufficient number of points in the recovery interval has not been obtained in previous studies. Results of the present study suggest that recovery from bronchial obstruction due to hyperventilation of cold air follows the same pattern as post-exercise recovery. Confirmation of this point is needed by a thorough characterization of the recovery interval from exercise- and hyperventilation-induced bronchial obstruction in the same subjects. Secondly, it has been shown that, as for exercise-induced asthma, tachyphylaxis following hyperventilation-induced asthma exists in some but

not all subjects [18, 19].

Although there was a broad between-subject variability, the pattern of recovery showed a high within-subject reproducibility. Moreover, the slopes of recovery were similar, even if different levels of bronchial obstruction were reached on each of the two occasions. This suggests that the kinetics of recovery is more dependent on individual factors (rate of deactivation of receptors or metabolism of mediators) than on baseline airway calibre and hyperresponsiveness or the level of the induced bronchial obstruction. Similar between-subject variability in the kinetics of recovery from bronchial obstruction due to histamine has been previously described [20]. Studying the slopes of recovery in the same individuals for several levels of bronchial obstruction, as has been done for histamine [20], would confirm that the kinetics of recovery is not linked with baseline airway calibre and hyperresponsiveness.

Our study has implications for the clinical or epidemiological assessment of bronchial hyperresponsiveness with hyperventilation of cold air. This work was a component of a series of steps, which represent an attempt to standardize this test through assessment of the within- and between-day reproducibility in asthmatic subjects [19], characterization of the shape of the dose-response curve [21] and demonstration that the dose-response curve is cumulative [22]. The exact timing for the assessment of airway calibre after the end of inhalation had not been determined. From the

results of the present study, maximal bronchial obstruction was reached 2–11 min after the end of the challenge. It would thus appear reasonable to assess airway calibre as soon as 2 min after the end of the challenge and to record it serially until it starts to increase.

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RÉSUMÉ: Nous avons étudié la cinétique de récupération de l'obstruction bronchique due à l'inhalation d'air froid sec chez 8 sujets asthmatiques. Lors de la première visite, nous avons mesuré le degré d'hyperexcitabilité bronchique à l'histamine. Lors des deux autres visites, après avoir obtenu la valeur de résistance pulmonaire (R_L) et la spirométrie de base, nous avons fait respirer de l'air froid sec (-20°C) durant 3 minutes. La R_L fut surveillée continuellement jusqu'à son retour à la valeur de base ($\pm 20\%$). La concentration d'histamine causant la chute de 20% du VEMS (CP₂₀) variait de 0.03 à 5.9 mg·ml⁻¹, ce qui correspondait à une large fourchette d'hyperexcitabilité bronchique. L'augmentation moyenne (± 1 écart-type) de la R_L fut de 2.03 ± 0.41 fois la valeur de base et fut atteinte 2–11 minutes après la fin de l'inhalation d'air froid. Il existait une corrélation linéaire hautement significative (valeurs de r² > 0.80 pour 14 des 16 droites) entre la R_L et le temps. Pour chaque sujet, la reproductibilité des deux récupérations étudiée par une analyse de covariance était bonne puisque les pentes des deux droites ne différaient pas significativement l'une de l'autre. Les pentes de récupération et le temps total de récupération (14 à 55 minutes) étaient très variables d'un sujet à l'autre. Nous n'avons observé aucune corrélation significative entre le calibre bronchique de base, le niveau d'hyperexcitabilité bronchique et l'augmentation maximale de la R_L d'une part et les pentes de récupération d'autre part. Nous concluons que la cinétique de récupération de l'obstruction bronchique due à l'inhalation d'air froid suit de façon satisfaisante un modèle linéaire. Il y a une grande variation des pentes de récupération d'un individu à l'autre mais une bonne reproductibilité lorsque le test est répété chez le même individu.