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Respiratory response to histamine- and methylcholine-induced bronchospasm in nonsmokers and asymptomatic smokers

J. Savoy*, M. Louis**, M.H. Kryger***, A. Forster****

Respiratory response to histamine- and methylcholine-induced bronchospasm in nonsmokers and asymptomatic smokers. J. Savoy, M. Louis, M.H. Kryger, A. Forster.

ABSTRACT: The respiratory response to bronchospasms of the same magnitude induced by inhalation of histamine or methylcholine was measured non-invasively, using bellow pneumographs, in nonsmokers and asymptomatic smokers. In each subject, tidal volume (V_T), breathing frequency (f) and inspiratory time (T_I) were obtained on two different days, in a randomized crossover fashion, with the following sequence: basal conditions, after inhalation of buffered saline as a control and after histamine or methylcholine inhalation. Basal and control conditions did not differ from each other and were the same for both groups. The respiratory responses to both bronchoconstrictors did not differ from each other and were also the same in both groups: V_T increased, f and T_I remained unchanged. Thus, V_T/T_I, an index of respiratory drive, also increased. In nonsmokers the increased V_T/T_I and the associated increase in minute ventilation were both correlated to the decrease in FEV_1. These correlations were not found in smokers. Although they have different effects on airway irritant receptors, inhaled histamine and methylcholine induce the same respiratory response in nonsmokers and smokers. Thus, the presumed smoking-related changes in airway mucosa permeability do not seem to influence the direct stimulating effect of histamine on these endings. The absence of correlation between FEV_1 and V_T/T_I changes in smokers suggests that smoking might affect the respiratory drive in acute drug-induced bronchospasm. *Eur Respir J. 1988, 1, 209–216.*

* Division de Pneumologie.
** Clinique Médicale Universitaire, Département de Médecine.
*** Department of Respiratory Medicine, St. Boniface General Hospital, Winnipeg, Manitoba, Canada.
**** Département d'Anesthésiologie, Hôpital Cantonal Universitaire, Geneva, Switzerland.

Correspondence: J. Savoy, Médecin-adjoint, Pneumologie, Hôpital Cantonal, CH 1700 Fribourg, Switzerland.

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In animals the respiratory responses to histamine and methylcholine inhalation differ [1]. Histamine induces rapid shallow breathing and affects the respiratory drive even when bronchoconstriction is prevented by prior bronchodilation [2]. In response to methylcholine, however, only slight changes in breathing pattern are observed, and the drive only increases in association with airway smooth muscle contraction [3]. These differences are thought to be due to the differential effects of these drugs on vagal receptors. Both can stimulate the irritant receptors indirectly, via airway smooth muscle contraction, while histamine has an additional direct chemical stimulating effect [4]. Comparison of the respiratory responses to both drugs might therefore be a good way of investigating the specific role of irritant receptors in the control of breathing in humans.

We recently analysed the respiratory response to bronchospasms of the same magnitude induced by histamine or methylcholine inhalation [5]. The data, obtained using standard respiratory equipment (mouthpiece, noseclip), showed that during bronchospasm the pattern of breathing was the same as in unobstructed resting ventilation and that the respiratory responses to histamine and methylcholine did not differ from each other, in terms of either drive or breathing pattern.

Since the respiratory apparatus used for these measurements could have an effect on the ventilation and pattern of breathing [6], we hypothesized that the failure to demonstrate a difference between histamine and methylcholine might be due to the superimposed effects of the mouthpiece and noseclip. We thought, therefore, that reassessment of the comparison using a non-invasive technique was justified.

Recent studies have also suggested that smoking affects the mucosal surface of airways and induces changes in airway epithelial permeability [7, 8]. These changes are associated with the opening of tight junctions. Since irritant receptors are located just beneath these junctions [9], we also hypothesized that these endings could be more directly exposed to inhaled drugs in smokers than in nonsmokers. Hence, in smokers, the direct chemical action of histamine on irritant receptors could be more pronounced and produce respiratory changes which would differ: 1) from those observed in nonsmokers, and 2) from those induced by methylcholine inhalation. Comparison of the response to histamine- and methylcholine-induced bronchospasm in smokers and nonsmokers

may contribute to the understanding of the role of irritant receptors in respiratory control in humans.

Materials and methods

Two groups of subjects were studied: eight normal nonsmokers and seven asymptomatic smokers matched for age and weight. In each subject the doses of histamine and methylcholine inducing similar significant decreases in forced expiratory volume in one second (FEV_1) were determined in a preliminary study. The experiment was then performed on two different days, in a randomized, crossover design. On each day FEV_1 and the respiratory parameters were obtained at three consecutive stages: 1) at baseline, 2) after inhalation of isotonic buffered saline as a control, and 3) after methylcholine or histamine inhalation.

Acetyl-beta-methylcholine (Sigma Chemicals, St. Louis, Mo.) and histamine phosphate (Sigma) were diluted in a 0.1 M sodium phosphate buffer (pH 7.3–7.4) which was used as a control solution. For both drugs, twofold increasing concentrations starting from 0.03 up to 32 $mg \cdot ml^{-1}$ were prepared [10]. To induce bronchoconstriction, the subjects first inhaled increasing concentrations of histamine at 8 minute intervals. On another day methylcholine was tested in similar conditions. Inhaled concentrations varied between 0.5 and 32 $mg \cdot ml^{-1}$ and were usually the same for both drugs. All the solutions were inhaled from the same nebulizer (De Vilbiss 646), powered with air at a flow of 8 $l \cdot min^{-1}$. The solutions were inhaled over ten consecutive inspirations from residual volume (RV) to total lung capacity (TLC). During each inhalation the respiratory pattern was controlled as follows: 5 s inspiration, 5 s breathhold and free expiration. During each inspiration the duration of drug delivery was set to 1.5 s using a breath-actuated system connected to the nebulizer.

The degree of bronchoconstriction was assessed by measuring FEV_1 using a spirometer (Vitalograph). The best of three successive values obtained at 30 s intervals was retained.

Tidal volume (V_T), as well as the relative contributions of the rib cage (RC) and of the abdomen (ABD) to the V_T were measured using a non-invasive technique as recently described [11]. Two air-filled rubber bellows (Pneumograph, model 108, Hewlett-Packard) were attached circumferentially around the chest at the level of the nipples and around the abdomen at the umbilical level. Any change in circumference of the chest or of the abdomen induced a linear variation of the corresponding bellow pressure. The pressures were measured using two differential transducers (model 267 BC, Hewlett-Packard), the signals of which were recorded on a 4-channel polygraph (Hewlett-Packard), and simultaneously stored and analysed on a microcomputer (Apple II Plus). The frequency response of the system, including the tubing used for connections, was flat up to 6 Hz.

The calibration of the pneumographs was performed using the least square method [12]. The subject, wearing a noseclip, was connected to a pneumotachograph (Fleisch No. 2) through a mouthpiece and was asked to produce V_T of different magnitudes, with different contributions of RC and ABD. During ten successive breaths the integrated signals of the pneumotachograph were collected simultaneously with the pressure signals from the bellows. These signals were sampled at 20 Hz, digitized, filtered and analysed by the microcomputer for computation of the calibration factors of RC and ABD, using linear regression analysis. These factors were then manually set through manipulation of the preamplifier gain of RC and ABD channels. The computer was also used for calculation of the means of the percentage difference between volumes obtained from the bellows and from the pneumotachograph. Calibration was accepted if this percentage difference was less than 10% over a wide range of V_T (about 200 to 1500 ml).

Respiratory frequency (f), minute ventilation ($\dot{V}_E$), inspiratory time (T_I), expiratory time (T_E), mean inspiratory flow (V_T/T_I), inspiratory fraction of the breath cycle (T_I/T_{tot}) and the relative contributions of RC and ABD to V_T were derived from the stored data. Changes in end-tidal volume (ETV) were derived from the changes in end-expiratory positions of RC and V_T.

The subjects were supine on a bed during all measurements and manipulations, including forced expiratory manoeuvres and aerosol inhalations. The rubber bellows attached around the chest and abdomen were taped to avoid any displacement. After calibration of the system, as well as before each period of recording, the subjects were allowed to rest for 2–3 min. Data were then collected over 5 min, everything being quiet in the room. No attention was paid to the route of breathing.

Statistical analysis

For the comparison between nonsmokers and smokers an unpaired t-test was used. Within each group of subjects the comparison between paired data was assessed using paired t-test. Analysis of variance for repeated measurements was used for testing differences between parameters obtained sequentially. $p < 0.05$ was considered statistically significant.

Results

Individual characteristics of the populations studied, nonsmokers and smokers, are presented in table 1. There was no significant difference between them in terms of age, height and body weight. The FEV_1 values differed in the two groups only when expressed as a percentage of predicted value.

Table 2A presents the individual values of FEV_1 and V_T for nonsmokers in the three experimental conditions associated with histamine or methylcholine inhalation. In response to histamine or methyl-

choline, the mean FEV_1 decrease in percent of control value (C) (±SD) was: 32.8 (17.2) and 34.9 (18.5) respectively. For the smokers, the same data are presented in table 2B. Here again the percent decrease in FEV_1 from the control value did not differ whether induced by histamine or methylcholine, 30.6±15.3 and 34.1±15.6 respectively. These changes were the same in both groups. When expressed in percent of predicted value (±SD) the mean FEV_1 was also the same in nonsmokers and smokers and after both bronchoconstrictors: 72.9 (22.8) and 63.7 (11.5) respectively after histamine, 69.4 (23.0) and 60.5 (16.2) respectively after methylcholine. For each corresponding experimental condition the mean VT was the same in both nonsmokers and smokers. In both groups there was no difference between baseline (B) and C, whereas a significant increase was observed following histamine and methylcholine inhalation.

Table 3 gives the mean values characterizing the timing of respiration for both nonsmokers and smokers. Between the two groups there was no significant difference in values obtained in B or C or during bronchospasm. Within each group these values were the same in B and C and did not change in response to histamine or methylcholine inhalation. Although TI looks somewhat longer in smokers than in nonsmokers, the difference is not significant.

Mean values for $\dot{V}E$ (±SD) at B before histamine and methylcholine were respectively: 6.93 (±1.25) and 6.89 (±1.25) *l* in nonsmokers and 7.06 (±1.43) and 7.13 (±1.41) *l* in smokers. These values were not different from each other and did not differ from the corresponding control data represented in figure 1. In nonsmokers mean VT/TI (±SD) in B was 377 (146) before histamine and 351 (113) $ml \cdot s^{-1}$ before methylcholine. In smokers it was 336 (82) and 343 (75) $ml \cdot s^{-1}$ respectively. Again, none of these values differed from each other and the data in the corresponding control conditions, as shown in figure 1, were statistically the same. The mean values for FEV_1 and the parameters representing the ventilatory response under control conditions and during bronchospasm are shown in figure 1. In response to a significant decrease in FEV_1 in the two groups studied, there was a similar significant increase in VT/TI and in $\dot{V}E$. The average spirograms for smokers and nonsmokers in response to histamine and methylcholine-induced bronchospasm are presented in figure 2. No difference could be noted between smokers and nonsmokers in their response to both drugs.

In nonsmokers, after histamine and methylcholine inhalation, the changes in $\dot{V}E$ and VT/TI were significantly correlated to the decrease in FEV_1 (fig. 3). However, in smokers, the changes in $\dot{V}E$ and VT TI, although of the same magnitude as in nonsmokers, were not correlated to the decrease in FEV_1 (fig. 3).

In both groups of subjects, the ETV did not change significantly in response to isotonic saline inhalation. In nonsmokers it increased significantly by 568 ml (±391) after histamine and by 338 ml (±256) after methylcholine. In smokers the corresponding mean values were 701 ml (±462) and 403 ml (±264). The relative RC contribution to the generation of the VT remained the same in each experimental stage. In control conditions before histamine inhalation, it was 39% (±17) and 37% (±11) in nonsmokers and smokers respectively, while before methylcholine it was 39% (±17) and 40% (±20) respectively. During histamine-induced bronchospasm, the data were 41% (±18) and 41% (±11) in nonsmokers and smokers respectively. The corresponding values after methylcholine inhalation were 39% (±17) and 44% (±14) respectively.

Table 1. - Characteristics of the studied populations (±SD)

	Nonsmokers	Smokers
n	8	7
Age yr	33.5±3.5	30.7±3.35
Weight kg	75.9±8.2	67.6±8.0
Height cm	181.6±8.0	177.1±3.9
FEV_1 *l*	4.94±1.43	3.82±0.69
FEV_1 % pred	110.3±14.1	92.4±13.7*
Smoking history packs/yr	–	10.8±2.1

* $p<0.05$

Discussion

Our results show that, in terms of breathing pattern, the respiratory responses to histamine and methylcholine inhalation did not differ from each other and were the same in smokers and nonsmokers. In terms of bronchoconstriction-related changes in drive, however, we observed a significant negative correlation between changes in FEV_1 and changes in VT/TI only in nonsmokers.

Validity of the comparisons

In both groups, the FEV_1 values obtained in B and after buffered saline inhalation were the same and, in bronchospasm, the magnitude of airflow obstruction obtained after histamine and methylcholine was identical. The effect of deep inspiration on bronchomotor tone during induced bronchospasm might have influenced the FEV_1 measurements in a different way in nonsmokers and smokers [13]. However, to our knowledge, it was never demonstrated that in asymptomatic smokers this effect is not the same as in normals. On the other hand, at each experimental stage, we measured FEV_1 three times, at 30 s intervals, retaining only the best value. In bronchospasm we did not observe any consistent change in the second or third value, as compared to the first one,

Table 2 . - Individual values of FEV_1 and V_T (±SD) at each experimental condition for nonsmokers and for smokers

Conditions	FEV_1 *l*								
	Subjects								
	1	2	3	4	5	6	7	8	x̄±SD
NonSmokers									
Baseline Before:									
- Histamine	5.0	5.55	5.3	3.5	3.0	4.6	4.71	4.60	4.53±0.87
- Methylcholine	5.1	5.2	5.12	3.2	2.95	4.75	4.74	4.3	4.41±0.87
Control Before:									
- Histamine	5.0	5.25	5.3	3.25	2.95	4.5	4.71	4.65	4.45±0.88
- Methylcholine	5.25	5.2	5.0	3.3	2.90	4.8	4.74	4.45	4.46±0.88
After Inhalation of:									
- Histamine	4.4	4.35	4.5	2.25	1.3	2.4	2.28	3.1	3.07±1.21
- Methylcholine	4.65	2.8	4.45	2.2	1.2	2.15	2.82	3.4	2.96±1.17
Smokers									
Baseline Before:									
- Histamine	4.52	4.33	3.53	2.85	3.15	3.61	4.37	–	3.76±0.65
- Methylcholine	4.26	4.44	3.52	2.90	3.15	3.45	4.59	–	3.76±0.67
Control Before:									
- Histamine	4.43	4.16	3.40	2.68	3.15	3.57	4.41	–	3.69±0.67
- Methylcholine	4.47	4.55	3.38	2.64	3.2	3.51	4.45	–	3.73±0.76
After Inhalation of:									
- Histamine	2.62	2.32	1.82	2.36	2.85	2.72	3.33	–	2.58±0.48
- Methylcholine	1.94	1.93	2.25	1.99	2.8	2.75	3.57	–	2.46±0.61
	V_T ml								
NonSmokers									
Baseline Before:									
- Histamine	586±80	724±99	867±92	490±77	357±84	643±95	444±63	713±199	603±168
- Methylcholine	534±70	506±53	894±84	524±75	426±85	528±151	480±93	604±190	562±143
Control Before:									
- Histamine	434±83	776±98	1000±125	435±85	308±85	704±95	490±93	581±155	591±224
- Methylcholine	506±95	608±53	1133±92	423±56	382±113	525±147	503±118	664±153	593±236
After Inhalation of:									
- Histamine	632±100	926±159	1022±64	684±141	638±148	930±117	638±146	489±120	745±188
- Methylcholine	584±69	785±110	1239±153	786±151	715±99	900±121	551±78	599±152	771±224
Smokers									
Baseline Before:									
- Histamine	755±207	707±142	381±66	483±74	432±45	913±100	769±90	-	634±201
- Methylcholine	1058±241	885±122	394±53	521±51	468±100	557±84	842±81	-	675±251
Control Before:									
- Histamine	1061±236	630±120	493±66	548±109	410±51	743±114	573±77	-	637±214
- Methylcholine	1387±170	780±112	409±56	525±57	519±83	567±98	740±109	-	704±328
After Inhalation of:									
- Histamine	1388±284	1565±368	690±119	881±148	567±105	1051±137	685±136	-	975±379
- Methylcholine	1160±206	1226±264	479±58	762±103	759±202	711±101	999±219	-	876±265

Table 3. - Breathing pattern parameters (±SD)

		Histamine			Methylcholine		
		BH	CH	H	BM	CM	M
f $l \cdot min^{-1}$:	NS	12.1 ± 2.3	12.1 ± 3.2	13.3 ± 4	12.7 ± 2.0	12.5 ± 2.7	13.0 ± 3.8
	S	12.4 ± 4.5	11.1 ± 2.7	11.1 ± 4.2	11.6 ± 3.6	10.0 ± 2.9	10.6 ± 3.3
Ti s:	NS	1.6 ± 0.3	1.6 ± 0.3	1.7 ± 0.5	1.6 ± 0.3	1.6 ± 0.3	1.7 ± 0.3
	S	2.0 ± 0.8	2.0 ± 0.5	2.2 ± 0.9	2.1 ± 0.7	2.2 ± 0.5	2.1 ± 0.6
Ti/T_{tot}:	NS	0.35 ± 0.08	0.33 ± 0.06	0.37 ± 0.06	0.35 ± 0.05	0.34 ± 0.04	0.37 ± 0.04
	S	0.37 ± 0.03	0.37 ± 0.04	0.38 ± 0.02	0.37 ± 0.03	0.36 ± 0.03	0.36 ± 0.05

f: frequency of breathing; Ti: inspiratory time; Ti/T_{tot}: inspiratory fraction of the breath cycle; NS: nonsmokers; S: smokers.

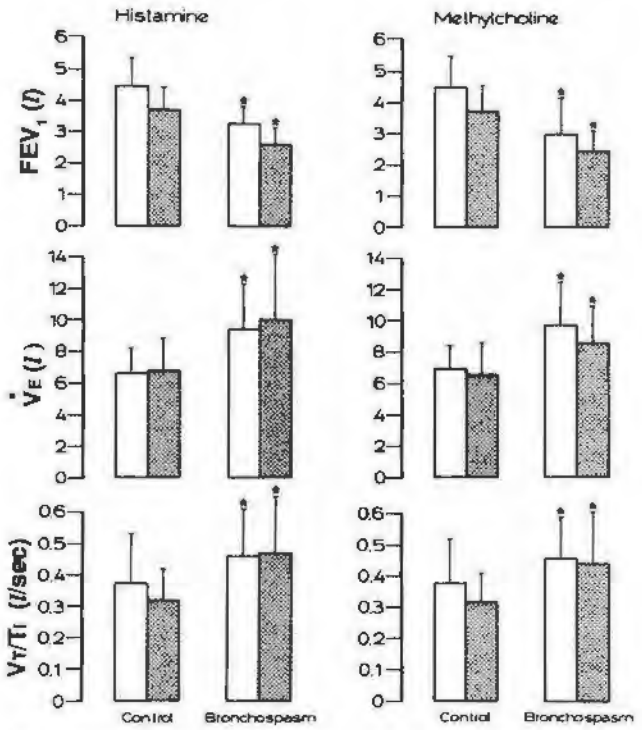

Fig. 1. Mean values (±SD) FEV_1, $\dot{V}E$ and VT/Ti in control conditions and in bronchospasm induced by methylcholine and histamine in nonsmokers (open columns) and smokers (dotted columns). * different from control, $p < 0.05$.

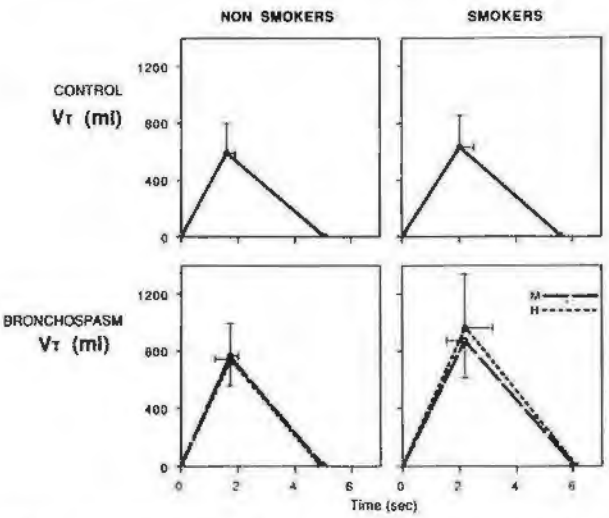

Fig. 2. Average spirogram for the two populations studied in control conditions and during bronchospasm. Ordinate: tidal volume in ml; abscissa: time in s. Dotted line: histamine; dashed line: methylcholine.

either in smokers, or in nonsmokers. This strongly suggests that the airway response to lung inflation was the same in both groups. Functional residual capacity (FRC) and TLC were not obtained in basal conditions in smokers. However, in the absence of any significant airway obstruction, these parameters can reasonably be expected to be in the normal range. This is supported by the fact that in a group of asymptomatic smokers tested by TOBIN *et al.* [14], TLC and FRC were normal. Furthermore, in both groups, in response to each bronchoconstrictor, the changes in ETV, the contribution of the RC to VT and to FRC did not differ. The above analysis therefore implies that the mechanical conditions associated with bronchospasm were the same in the two groups, for both histamine and methylcholine.

The concentrations of histamine and methylcholine used in each subject did not differ from each other. To avoid non-specific pH effect on airway receptors, the drugs were diluted in buffered saline [15]. Some of the subjects experienced flushes, headache and the sensation of tracheal burning after histamine inhalation. However, the systemic effects probably did not influence the results, since earlier studies suggest they do not affect the control of breathing [16].

Arterial partial pressures of oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) were not measured. We can safely assume they were normal in resting conditions B and C. During bronchospasm, Pa_{CO_2} was probably normal or low, since increased Pa_{CO_2} is seen only in severe asthma with fatigue of the respiratory muscles, which obviously did not occur in our experiments.

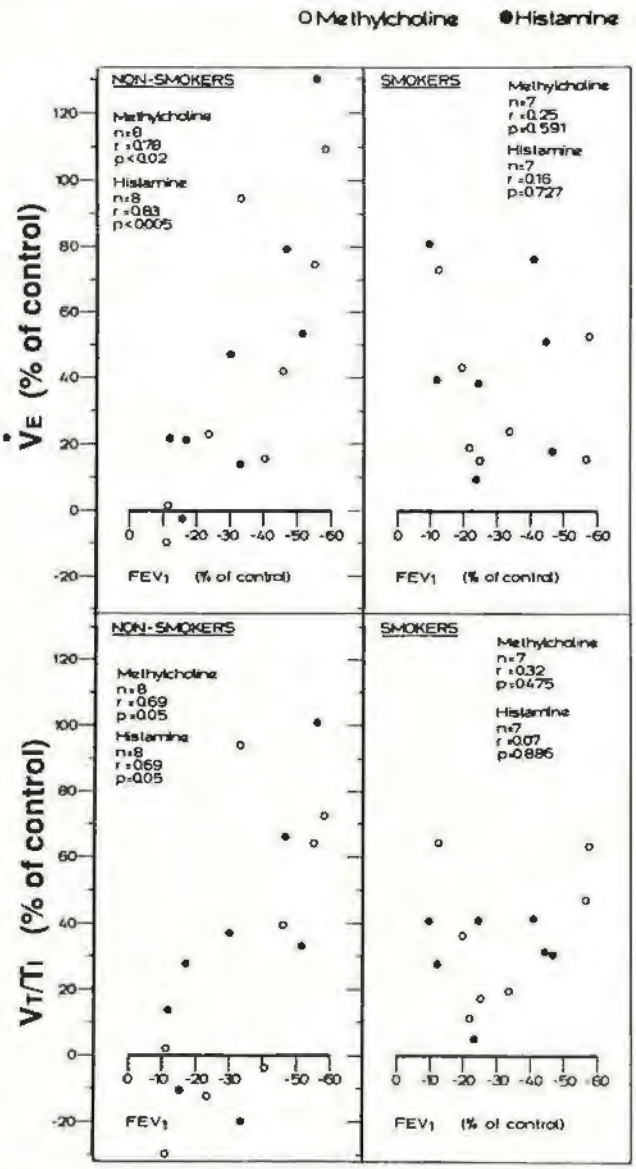

Fig. 3. Relationships between changes in FEV_1 and changes in $\dot{V}E$ (upper panels), and in VT/TI (bottom panels) induced by methylcholine (○) or histamine (●) inhalation. Abscissa: FEV_1; ordinate: $\dot{V}E$, VT/TI. Left panels: nonsmokers; right panels: smokers. All parameters are expressed as a percentage of the control value.

Pa_{O_2}, however, could have fallen in the case of severe bronchospasm. The degree of hypoxia and its role are difficult to visualize, but they probably did not affect the comparison. Firstly, in the presence of a normal Pa_{CO_2}, the hypoxic drive is effective only at a Pa_{O_2} of 70 mmHg or less [17]. Secondly, in similar studies, using methylcholine, it has been shown that a 75% decrease in specific airways conductance does not affect the arterial oxygen saturation and that an 84% decrease induces only a slight hypoxaemia [18]. Finally, it is reasonable to think that the hypoxic drive was the same in response to both drugs and in both groups, since mechanical changes were the same.

We can therefore be reasonably confident that our study really compares the local effects of histamine and methylcholine on vagal airway receptors in normal subjects and asymptomatic smokers.

Resting breathing pattern

Among the breathing pattern parameters observed in our non smoking subjects, the frequency of breathing was lower than in other studies using non-invasive techniques [14]. Several factors need to be considered in identifying the reason for such a difference. The bellow pneumotachograph technique has been carefully validated and was checked against inductive plethysmography [11]. However, in our technique, only thin, light strings are attached around the chest and the abdomen, while, in inductive plethysmography, the subject is wrapped in two large pieces of elastic tissue. Our technique also markedly differs from the canopy system [19, 20]. The time spent on data acquisition might also have played a role. For example, it was 5 min in our study, 15 min in the study by CHADHA *et al.* [18], while LOVERIDGE *et al.* exposed their subjects to a 45 min recording period [21]. On the other hand, it was shown by GILBERT *et al.* that, in this kind of study, data obtained during the second minute are representative of the rest of the recording [6]. The type of subjects selected for the study certainly plays a major role. Ours were all physicians or medical students, some of them being familiar with the techniques of respiratory physiology. Although they did not know the purpose of the study they were certainly less affected by stress than completely naive subjects. This is supported by the fact that studies using the same technique in the same laboratory gave results similar to the present ones in initiated subjects, and data similar to those of the literature in completely naive subjects [11, 22].

The pattern of breathing of the smokers was different from that given by TOBIN *et al.* [23]. In a group of 22 asymptomatic smokers, as compared to normal nonsmokers of the same age, they found significant increases in f, VT, $\dot{V}E$ and VT/TI, while TI and TI/T_{tot} were smaller. In the present study smokers did not differ from nonsmokers. Again, this could result from subject difference only, since our smokers were all physicians. It is interesting to note that in smokers, f was somewhat lower and VT somewhat larger than in nonsmokers, although height and body weight in smokers were slightly (but not significantly) lower. We have no explanation for this trend. We must mention, however, that we did not pay attention to the delay between the last cigarette and the testing of the subject, or to the route of breathing [24, 25].

Adaptation to bronchospasm

Our data indicate that, in normal nonsmokers, bronchospasm induces an increase in VT/TI which is proportional to the decrease in expiratory flow. This finding is in accordance with the results of previous studies performed using standard equipment, which

show an increased mouth occlusion pressure which correlates with the magnitude of the obstruction in response to methylcholine as well as to histamine inhalation [5]. The consequences of such a drive increase differ. Using invasive techniques, $\dot{V}E$ remained unchanged or was slightly increased, while in this case, it increased in proportion to the magnitude of the obstruction. As Ti and f remained unchanged this increase can be attributed entirely to changes in drive. During each inspiration of the same duration as in C, the pressure generated by the inspiratory muscles increases, producing larger Vt than at rest.

In terms of breathing pattern, the present study also agrees with our previous 'invasive' experiments in man. In nonsmokers, unlike animals, the response to histamine does not differ from the response to methylcholine [5]. This study only shows that this is also true for asymptomatic young smokers. Interestingly, the responses to histamine and methylcholine follow exactly the same patterns as the responses to methylcholine proposed by CHADHA *et al.* [18]. It is therefore safe to conclude that in man, the major response to acute drug-induced bronchospasm is an increased respiratory drive, not a change in the pattern of breathing.

This observation further suggests that in bronchospasm, mouthpiece and noseclip interfere with the measurements of the drive, but not with the measurements of the pattern of breathing, since the only difference between the results obtained using both techniques is the change in $\dot{V}E$ in response to bronchoconstriction. While in normal resting conditions mouthpiece and noseclip stimulate the ventilation, they probably blunt the respiratory response to acute induced bronchospasm.

Mechanisms involved in the respiratory response to bronchospasm

The absence of any difference between histamine and methylcholine in normal subjects, for a similar magnitude of obstruction, mechanical conditions and Vt, suggests that the mechanisms involved in the respiratory adaptation to hoth drugs are the same. Studies using local airway anaesthesia have clearly shown that, under these experimental conditions, the role of airway vagal endings in modulating the respiratory response is significant [3]. One can therefore conclude that the stimulating effect of histamine and methylcholine on these receptors was identical for both types of bronchospasm. Since recent data suggest that inhaled histamine has direct stimulating effects on airway irritant receptors [26], the present findings imply that only receptors indirectly stimulated via airway smooth muscle contraction play a role in the regulation of the pattern of breathing and drive in induced bronchospasm in normals. They confirm our previous data using invasive standard respiratory equipments.

To our knowledge, the opening of epithelial tight junctions associated with smoking has never been definitely documented in humans. The fact that smoke inhalation induces an increase in epithelial permeability for histamine in man as in animals strongly suggests that it really occurs [27]. Thus one can assume that the bronchial mucosa of smokers is in a more favourable condition for direct chemical action of inhaled drugs on vagal endings than that of the nonsmokers. The absence of any difference in respiratory response between histamine and methylcholine in smokers further supports our conclusions about indirect involvement of the vagal airway irritant receptors suggested by the data in nonsmokers.

Our study shows that the breathing pattern associated with bronchospasm is the same in smokers as in nonsmokers, while the way smokers adapt to bronchospasm in terms of respiratory drive differs. Indeed, unlike nonsmokers, their Vt/Ti does not correlate to the decrease in FEV_1. This is intriguing, since both responses are vagally-mediated. A partial explanation can be found in the fact that breathing pattern regulation involves both irritant and stretch receptors, while probably only the former contribute to the drive changes observed in bronchospasm. It follows that in aysmptomatic smokers some dysfunction of irritant receptors has to be present. A recent study by PARDY *et al.* shows that histamine inhalation modifies the pattern of breathing in normocapnic chronic obstructive patients without affecting the drive as expressed as Vt/Ti [28]. Furthermore, the recent study by OLIVEN *et al.* [29] establishes that in chronic obstructive lung disease, methylcholine inhalation is associated with an increase in drive which only depends on the chemical control of breathing. These data clearly imply that, in terms of drive, vagal airway receptors do not significantly contribute to the adaptation to acute induced bronchospasm in chronic obstructive lung disease. From the above analysis one could therefore propose the hypothesis that, in young asymptomatic smokers, some smoking-related alterations of the mucosa of the airways are associated with a dysfunction of vagal irritant receptors, which might precede the appearance of chronic obstructive pulmonary disease. It might be that this is an early manifestation of chronic bronchitis, or chronic airway obstruction.

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RÉSUMÉ: L'histamine et la méthylcholine ont des effets différents sur les récepteurs vagaux bronchiques à l'irritation. La première les stimule par une action chimique directe et indirectement par le biais du bronchospasme, tandis que la seconde n'a qu'un effet indirect. Afin de tenter d'identifier le rôle de ces afférences dans le contrôle ventilatoire chez l'homme, nous avons comparé les réponses respiratoires au bronchospasme induit par inhalation d'histamine ou de méthylcholine chez des sujets normaux et des fumeurs asymptomatiques. Le choix d'un groupe de fumeurs se justifie par l'hypothèse qu'une augmentation de perméabilité de l'epithélium bronchique devrait faciliter l'accès de l'histamine vers les terminaisons nerveuses, accroître ainsi son action directe et produire par conséquent des effets différents de ceux attendus chez les non-fumeurs, et différents de ceux induits par la méthylcholine. Huit sujets normaux et sept fumeurs asymptomatiques furent testés. L'expérience était exécutée sur deux jours différents, selon la technique du contrôle croisé. Chaque jour, le VEMS ainsi que le volume courant (V_T), la fréquence (f) et la durée de l'inspiration (T_I) étaient déterminés lors de trois étapes successives: 1) en condition basale; 2) en condition de contrôle après inhalation d'une solution saline isotonique tamponnée; 3) après induction d'un bronchospasme par inhalation d'histamine ou méthylcholine. Les paramètres respiratoires étaient mesurés de façon non-invasive à l'aide de la technique des pneumographes à soufflet. La ventilation par minute ($\dot{V}_E$), le débit inspiratoire moyen, index de la commande respiratoire (V_T/T_I) et la fraction inspiratoire du cycle respiratoire (T_I/T_{tot}) étaient obtenus par calcul à partir des données enregistrées sur ordinateur. En réponse à l'inhalation d'histamine ou de méthylcholine, chez les fumeurs comme chez les non-fumeurs, aucun changement de mode ventilatoire ne fut observé. Par contre, en réponse aux deux substances, pour un bronchospasme de même intensité, V_T et, par conséquent, $\dot{V}_E$ augmentaient significativement et dans la même proportion chez les deux groupes testés. Chez les non-fumeurs, on observait, en outre, une relation significative entre la chute du VEMS et l'augmentation de $\dot{V}_E$ et V_T/T_I. Chez les fumeurs, une telle corrélation n'était pas présente. Ces résultats suggèrent que l'histamine et la méthylcholine ont le même effet stimulateur sur les récepteurs à l'irritation des voies aériennes. Ceci indique que seules les afférences stimulées indirectement par le biais de la contraction de la musculature lisse bronchique sont impliquées dans la réponse au bronchospasme aigu, que ce soit pour l'adaptation de la commande ou du mode ventilatoire. L'absence de corrélation entre l'intensité du bronchospasme et le changement de commande ventilatoire chez les fumeurs asymptomatiques suggère que la fumée induit une dysfonction des récepteurs à l'irritation qui pourrait précéder l'apparition de la maladie obstructive chronique ou de la bronchite chronique.