Airway responsiveness to methacholine and deep inhalations in subjects with rhinitis without asthma

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Background: Airway hyperresponsiveness in asthma is believed to be caused in part by the inability of deep inspirations to modulate airway narrowing.
Objective: We investigated whether deep inspirations taken before or after methacholine inhalation attenuate bronchoconstriction in subjects with rhinitis. The results were compared with a group of healthy subjects.
Methods: Ten subjects with rhinitis without asthma and 10 healthy subjects were studied on 3 different occasions at random. Bronchial challenges were performed with a single dose of methacholine known to decrease the FEV_1 by 17% to 40%. Challenges were performed with avoidance of deep inspirations, or with 5 deep inspirations preceding or following the inhalation of methacholine. Lung function measurements were specific airway conductance, forced expiratory flow at 30% to 40% of vital capacity on a maneuver started from end-tidal inspiration (partial flow), and residual volume (partial residual volume).
Results: In healthy subjects, deep inspirations taken after methacholine caused less changes in specific airway conductance, partial flow, and partial residual volume ($P < .005$ for all) than deep inspirations taken before methacholine or avoidance. In subjects with rhinitis, methacholine produced similar functional changes independently of the presence or absence of any deep inspirations. Compared with normal subjects, the attenuating effects of deep inspirations after methacholine on partial flow and partial residual volume were blunted in the subjects with rhinitis ($P = .02$ and $P = .05$, respectively).
Conclusion: The ability to dilate methacholine-constricted airways by deep inspirations is impaired in subjects with rhinitis, possibly because of an abnormal behavior of airway smooth muscle. (J Allergy Clin Immunol 2008;121: 403-7.)

Key words: *Methacholine challenge, bronchodilatation, bronchoprotection, spirometry, airway conductance, partial expiratory maneuver*

Subjects with allergic rhinitis are considered to be at an increased risk for developing asthma,[1] mainly because they often have lower airway inflammation similar to that of subjects with asthma[2] and borderline airway hyperresponsiveness. In 1981, Fish et al[3] showed that airway responsiveness to methacholine (MCh) of subjects with hay fever was similar to that of healthy subjects when measured by FEV_1 but similar to that of subjects with asthma when measured by specific airway conductance (sGaw). This suggested that the airway smooth muscle (ASM) of subjects with rhinitis responded to the constrictor stimulus as much as the asthmatic ASM, but the response was ablated in the former by the full inflation necessary to measure FEV_1. Similar findings have been reported by Crimi et al[2] by comparing maximal and partial flow-volume curves in patients with rhinitis and asthma. More recently, Pyrgos et al[4] showed that repeated deep inspirations (DIs) taken before MCh inhalation attenuated the decrease in FEV_1 in a similar manner in subjects with rhinitis and healthy subjects, thus suggesting a bronchoprotective effect of DIs in both groups. Collectively, these observations would suggest that the ASM of subjects with rhinitis may behave differently from normal ASM, but this difference is masked during routine bronchial challenges by the effects of DIs used to inhale MCh,[5] or the FEV_1 maneuver, or both. As a matter of fact, DIs taken before the inhalation of the constricting agent could blunt the response by altering the length adaptation of ASM, thus readapting the internal contractile structures in a way that they can generate less force,[6] whereas DIs taken immediately after the inhalation of the constricting agent could also reduce the airway smooth muscle tone by breaking down actin-myosin cross-bridges.[7] Therefore, bronchial challenges using full lung inflations to inhale MCh[8,9] and measurements of FEV_1[10] are difficult to interpret in terms of ASM dynamics.

The aim of the current study was to identify whether differences in airway constrictor responses to MCh exist between subjects with rhinitis and healthy subjects by looking at the effects of DIs on airway caliber. For this purpose, we used lung function measurements that do not require full lung inflation and an inhalation protocol during quiet tidal breathing after avoidance of spontaneous deep breaths or sighs.

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Abbreviations used
ASM: Airway smooth muscle
DI: Deep inspiration
FVC: Forced vital capacity
MCh: Methacholine
$\dot{V}$part: Expiratory flow at 30% to 40% of vital capacity from a forced maneuver started from end-tidal inspiration
RVpart: Residual volume after a partial expiration
sGaw: Specific airway conductance

METHODS

Subjects and study protocol

Ten subjects with rhinitis and 10 healthy subjects were studied (Table I). All subjects with rhinitis were allergic and had mild symptoms, 6 perennially and 4 seasonally. The disease condition was diagnosed according to the recent guidelines.[1] Those with seasonal symptoms were studied out of pollen season. No subject was taking any medications such as antihistamines or nasal corticosteroids at the time of the study. All subjects attended the laboratory on 5 to 6 occasions. On a screening day, a questionnaire for asthma symptoms was administered to include only subjects who had never experienced symptoms suggestive for asthma at rest or with exercise. Spirometry and a routine MCh challenge were then obtained. On 1 or 2 prestudy days, a single provocative dose of MCh causing at least 15% FEV_1 fall after 10-minute DI avoidance was determined (control challenge). This dose was then used on 3 randomized study days, separated by 2 to 7 days, 1 with prohibition of any DIs (no-DIs day), 1 preceded (DIs-pre day), and 1 followed by 5 DIs (DIs-post day). On all study days, care was taken to ensure that no subject took sighs or DIs unless requested per protocol.

Study protocol was approved by the internal Ethics Committee, and each subject gave informed consent.

Lung function measurements

Mouth flow was measured by a mass flowmeter (SensorMedics, Yorba Linda, Calif), and volumes were obtained by numerical integration of the flow signal. FEV_1 and forced vital capacity (FVC) were measured according to the American Thoracic Society-European Respiratory Society guidelines.[11] Airway resistance was measured by body plethysmography (Vmax 6200 Autobox; SensorMedics) while the subject was panting slightly >1.7 Hz. Once 3 to 4 acceptable measurements of airway resistance were obtained, thoracic gas volume was measured by panting against a closed shutter at a frequency slightly <1 Hz, and sGaw was calculated as 1/(thoracic gas volume × airway resistance). Soon after the opening of the shutter, the subjects expired forcefully from end-tidal inspiration down to residual volume (RVpart) to obtain a partial flow-volume curve for measurements of forced expiratory flow at a constant absolute lung volume (part) between 30% and 40% of control FVC.

Bronchial challenges

Solutions of MCh were prepared by adding distilled water to dry powder MCh chloride (Laboratorio Farmaceutico Lofarma, Milan, Italy). Aerosols were delivered by an SM-1 Rosenthal breath-activated dosimeter (SensorMedics) driven by compressed air (30 lb/in^2) with 1-second actuations and an output of 10 μL per actuation. All doses of MCh were inhaled during quiet tidal breathing in a sitting position. For the routine challenge on screening days, increasing doses of MCh from 0.02 to 1.2 mg were inhaled by using 1 mg/mL and 10 mg/mL concentrations and changing the number of breaths. FEV_1 was measured between 30 seconds and 60 seconds after each dose. For study days, the MCh doses determined at control challenge were obtained by using a 50-mg/mL concentration with an appropriate number of breaths between 5 and 20. The response to MCh was assessed by using parameters not requiring full lung inflation and regarded as sensitive to changes occurring at different levels of the bronchial tree, namely, sGaw, $\dot{V}$part, and RVpart. On each study day, sGaw, $\dot{V}$part, RVpart, FEV_1, and FVC were measured in this order at baseline. Then, after 10 minutes of tidal breathing with prohibition of DIs or sighs, only those parameters not requiring a full lung inflation, namely, sGaw, $\dot{V}$part, and RVpart, were again measured immediately before (control) and within 2 minutes after MCh inhalation (Fig 1). DIs before or after MCh were always taken through the mouth over a period of 30 seconds.

TABLE I. Anthropometric and lung function data at screening

Subjects	Healthy	Rhinitic
No.	10	10
Age (y)	27 ± 6	33 ± 10
Sex, male/female	6/4	9/1
BMI (kg/m^2)	23 ± 3	26 ± 4
FEV_1 % predicted	108 ± 10	107 ± 11
FVC % predicted	110 ± 10	108 ± 11
FEV_1 fall*, %	4 ± 2	5 ± 2
Allergic sensitization		HDM (4), grass (2), *Parietaria* (4)

BMI, Body mass index; *HDM*, house dust mite.
*At cumulative 2400 μg MCh.

Statistical analysis

On each study day and for any lung function parameter, the response to MCh challenge was expressed as percent of baseline. Differences between study days within groups were compared using a 1-way ANOVA with Newman-Keuls *post hoc* test. When a significant effect of DIs on a given parameter was detected, differences between groups were compared by applying an unpaired *t* test to a relaxation index calculated as follows: $([X_{control} - X_{MCh}]/X_{control})_{no\text{-}DIs} - ([X_{control}\text{-}X_{MCh}]/X_{control})_{DIs}$, where X denotes the parameter, the first term denotes the fractional changes observed on the no-DI day, and the second term those observed on a DIs day. Values range from −1 to +1, with low numbers for sGaw, $\dot{V}$part and high numbers for RVpart denoting impaired bronchodilatation with the DIs. An example of calculation of the relaxation index is shown in Fig 2. *P* values <.05 were considered statistically significant. Data are expressed as means ± SDs.

RESULTS

On screening days, baseline lung function data were similar between subjects with rhinitis and healthy subjects (Table I). No subject of either group responded to the routine MCh challenge at the maximal cumulative dose of 2400 μg. The single dose of MCh to be used for study days was 8000 ± 4830 μg in subjects with rhinitis, not significantly different from the 7250 ± 2993 μg used in healthy subjects ($P = .68$). These doses caused similar FEV_1 decrements of 30% ± 12% and 34% ± 12%, respectively ($P > .52$). Baseline lung function was not different between groups and study days (Table II). The control values for sGaw, $\dot{V}$part, and RVpart, measured after 10-minute prohibition of deep breaths or sighs, were not significantly different from baseline ($P > .80$ for all).

On the no-DI days, the single dose of MCh caused decrements of sGaw, $\dot{V}$part, and increments in RVpart (Table III) similar between subjects with rhinitis and asthma ($P > .15$ for all). On the DI-post days, the MCh-induced reductions in sGaw ($P < .0005$) and $\dot{V}$part ($P = .0006$) and the increase in RVpart ($P = 0.0002$) were attenuated in healthy subjects but not in subjects with rhinitis ($P > .22$ for all). The relaxation indexes for $\dot{V}$part and RVpart calculated between no-DI and DIs after MCh days were significantly different between healthy subjects and subjects with rhinitis ($P = .02$ and $P = .05$, respectively; Fig 3), thus suggesting that the DIs

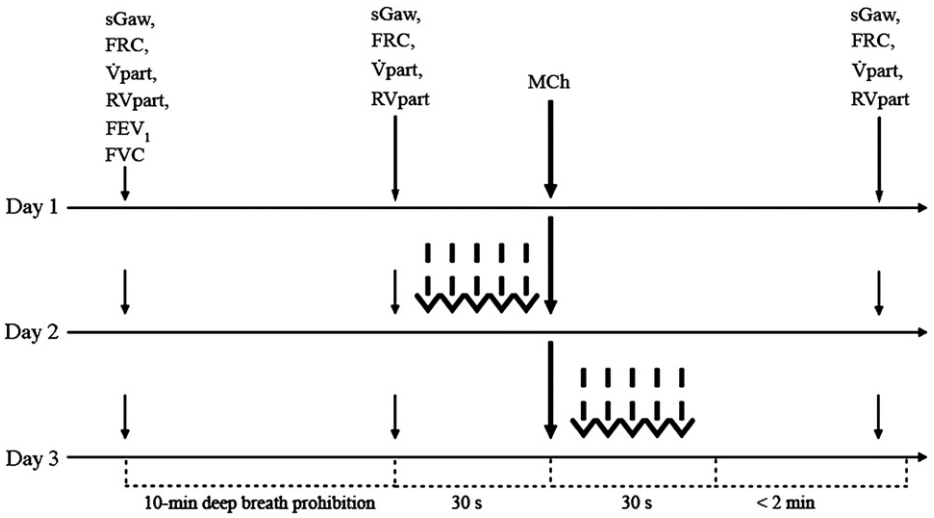

FIG 1. Sequence of measurements and treatments with 5 DIs *(interrupted downward arrows). FRC,* Functional residual capacity.

taken after MCh in the patients with rhinitis were ineffective in modulating the decrease in V̇part and increase in RVpart compared with the healthy subjects. In contrast, the relaxation index for sGaw was not significantly different between subjects with rhinitis and healthy subjects ($P = .57$). On the DI-pre days, the MCh-induced changes in sGaw, V̇part, and RVpart were not significantly different from the no-DI days either in healthy subjects or subjects with rhinitis ($P > .13$ for all).

DISCUSSION

The main finding of this study is that in subjects without asthma with allergic rhinitis and normal response to a standard MCh challenge, the ability of DIs to relax constricted airways was blunted compared with healthy subjects. A secondary finding, which confirms and extends a previous study,[12] is that neither in subjects with rhinitis nor in healthy subjects did DIs taken before MCh inhalation attenuate the response as measured by lung function parameters not requiring a previous inspiration to total lung capacity.

In 1976, Fish et al[13] showed that the response to MCh in patients with rhinitis was similar to healthy subjects when assessed by FEV_1, but worse and similar to patients with asthma when assessed by sGaw. In a further study from the same group, it was suggested that the bronchoconstrictor responses in subjects with rhinitis may be greatly attenuated by lung inflation.[3] In the current study, neither subjects with rhinitis nor healthy subjects responded to a standard MCh challenge, which would be consistent with a potent bronchodilator effect of the full inflation maneuvers required to measure FEV_1 in both groups. Moreover, the response to a single MCh dose with DIs avoidance was also similar between groups, a finding that may appear at variance with those of the first study by Fish et al.[13] An important difference that may explain this discrepancy is that DIs or sighs were strictly prohibited for 10 minutes before and throughout the bronchial challenge in the current but not in their study, where each MCh dose was inhaled with 5 deep breaths and measurements of FEV_1 were obtained after each dose increment. As shown in the current study, repeated DIs after inhalation of MCh can relax airways in healthy subjects but not in subjects with rhinitis. Thus, a possible explanation for the difference between our data and the data of Fish et al[13] is that in their study, the effect of MCh was ablated after each dose increment by full lung inflations in healthy subjects but not in subjects with rhinitis.

The lack of relaxing effect of DIs taken after MCh in patients with rhinitis of the current study may also appear at variance with the second study by Fish et al,[3] in which it was shown that a single DI after MCh was able to relax constricted airways in subjects with rhinitis but not in subjects with asthma. In that study, however, sGaw increased at 7 seconds after a DI but returned to the preinspiration values during a 60-second observation time, which is consistent with the results of the current study, in which lung function measurements were taken approximately 1 minute after the last DI.

To explain why multiple DIs taken after MCh inhalation ablated MCh induced bronchoconstriction in healthy subjects but not in subjects with rhinitis, several mechanisms must be considered. In healthy human beings exposed to a constrictor agent, taking a DI is known to produce bronchodilatation, likely as the result of the mechanical inflating stimulus applied to the airway wall and capable of stretching the airway smooth muscle.[7,14-16] As a first hypothesis, the blunted effects of the DIs in our patients with rhinitis could be explained by an ineffective stretching of airways by DIs. Yet this hypothesis does not take into consideration of the similar effects of MCh on the FEV_1, a maneuver that is preceded by a DI, between subjects with rhinitis and healthy subjects in both our study and the study by Fish et al.[3] Alternatively and more likely, the reduced bronchodilator effects of the DIs in the subjects with rhinitis could be ascribed to a faster airway reconstriction after a DI in the patients. After reducing bronchial tone as with a DI, narrowing reoccurs at a rate presumably depending on the ASM velocity of shortening. In healthy human beings exposed to a dose of MCh, a single DI causes a decrease in airway or lung resistance that recovers to the pre-DI values in about 1 to 2 minutes. In subjects with asthma, the recovery is much faster, thus suggesting premature reoccurrence of airflow obstruction.[15,17-19] With more DIs or exercise hyperventilation, the effects on airway caliber last longer in both healthy subjects[16] and subjects with asthma.[20] On the basis of these observations, it can be hypothesized that the lack of persistent relaxant effect in subjects with rhinitis might be a result of a

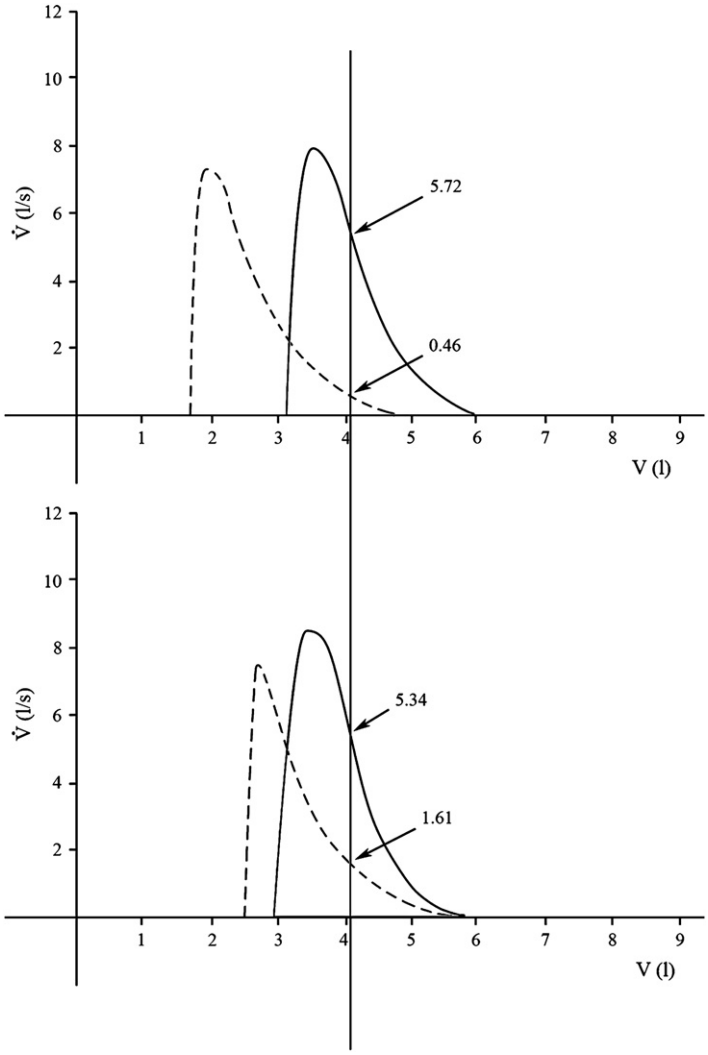

FIG 2. Example of calculation of part and relaxation index. Partial expiratory flow/volume curves on no-DIs day *(upper panel)* and on DIs-post day *(lower panel)* before *(continuous lines)* and after methacholine challenge *(dashed lines)* are shown. The vertical line indicates the constant absolute volume of 30% control FVC at which V̇part has been measured. Relaxation index is calculated as follows: ([5.72- 0.46]/5.72) – ([5.34-1.61]/5.34) = 0.22.

faster recovery of contractile force. Indeed, a major difference between our subjects with rhinitis and healthy subjects was the allergic sensitizations in the former. *In vitro*, sensitized airway smooth muscle showed an increased velocity of shortening compared with nonsensitized muscles.[21] Further studies are needed to support this interpretation.

Prohibition of deep breaths before MCh caused similar bronchoconstrictor responses in subjects with rhinitis and healthy subjects, who did not respond to a standard MCh challenge. The enhanced responsiveness by avoidance of deep breaths can be explained by adaptation of airway smooth muscle at a length at which the interaction between contractile elements is enhanced.[6] However, the finding that 5 DIs taken before MCh had no effect on either healthy subjects or subjects with rhinitis does not support the possibility of differences in length adaptation between the airway smooth muscle of healthy subjects and subjects with rhinitis. The lack of protective effect of deep breaths taken before MCh confirms and extends the results of a previous study from our group showing that a bronchoprotective effect can be observed in healthy subjects using FEV_1 and FVC but not lung function measurements free of full lung inflation.[12] As previously discussed in depth,[12] this difference may reflect an enhancement of airway wall distensibility rather than a reduced contractility of airway smooth muscle by deep breaths. It is therefore reasonable to assume that the bronchoprotective effect of deep breaths reported by Scichilone et al[10,22] in both healthy subjects and subjects with rhinitis was dependent on the full lung inflation required to measure FEV_1 and FVC.

Other active mechanisms have been invoked to explain the efficacy and duration of the deep breaths. One of the putative molecules capable of reducing airway smooth muscle tone is nitric oxide,[23,24] which is possibly increased in subjects with allergy. Although not measured in the current study, we do not believe that nitric oxide had a role in explaining our results, because the responses to MCh in the absence of any deep breaths or with the deep breaths taken before the challenge were similar

TABLE II. Baseline lung function data on study days*

Study day	No DIs	DIs before MCh	DIs after MCh
Rhinitic			
sGaw, $cmH_2O^{-1}\ s^{-1}$	0.21 ± 0.06	0.22 ± 0.06	0.21 ± 0.05
$\dot{V}$part, L/s	3.06 ± 1.49	3.12 ± 1.62	3.21 ± 1.27
RVpart, L	1.65 ± 0.55	1.76 ± 0.48	1.79 ± 0.66
FEV_1, L	4.20 ± 0.96	4.14 ± 1.01	4.13 ± 0.97
Healthy			
sGaw, $cmH_2O^{-1}\ s^{-1}$	0.20 ± 0.03	0.21 ± 0.03	0.21 ± 0.03
$\dot{V}$part, L/s	2.85 ± 0.99	2.92 ± 0.72	2.81 ± 0.89
RVpart, L	1.45 ± 0.25	1.35 ± 0.25	1.45 ± 0.33
FEV_1, L	4.21 ± 0.78	4.32 ± 0.83	4.20 ± 0.83

*There were no significant differences between days and groups.

TABLE III. Percent changes of control of the main lung function data after single-dose MCh on the 3 study days

Study day	No DIs	DIs before MCh	DIs after MCh
Rhinitic			
sGaw, % of control	29 ± 14	31 ± 16	40 ± 21
$\dot{V}$part, % of control	7 ± 12	10 ± 11	12 ± 13
RVpart, % of control	174 ± 30	162 ± 46	154 ± 42
Healthy			
sGaw, % of control	28 ± 10	31 ± 13	47 ± 19*
$\dot{V}$part, % of control	3 ± 3	9 ± 8	27 ± 17*
RVpart, % of control	199 ± 43	183 ± 63	143 ± 43*

*Significantly different from No-DIs and DIs before MCh.

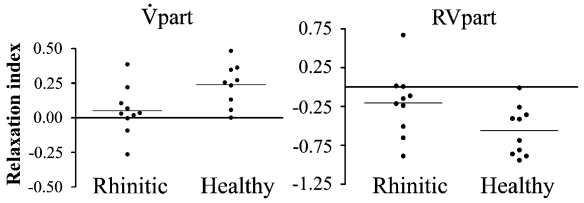

FIG 3. Relaxation indexes for $\dot{V}$part and RVpart in subjects with rhinitis and healthy subjects calculated as fractional differences between no-DI and DIs after MCh days ($P = .02$, and $P = .05$, respectively).

between subjects with rhinitis and healthy subjects. Yet it remains to be established whether nitric oxide could differently increase in healthy subjects and subjects with rhinitis with the deep breaths taken after airway narrowing is already induced.

In conclusion, the current study shows that the relaxing effect of repeated DIs on constricted airways is impaired in subjects with allergic rhinitis who never experienced asthma symptoms and did not respond to a standard MCh challenge. It is suggested that the difference in response to DIs between healthy subjects and subjects with rhinitis is a result of a difference in the shortening velocity of airway smooth muscle, presumably related to allergic sensitization, rather than an impaired short-lived effect of the DI on airway mechanics. Finally, we are well aware that our data cannot allow us to conclude whether this anomalous behavior of the airways is just an epiphenomenon of the rhinitic condition or represents a mechanism through which asthma may develop with time in these patients. Further longitudinal studies are necessary to clarify this issue.

Clinical implications: Whether this represents a risk factor for developing bronchial asthma in patients with rhinitis is not proven by the current data and needs to be established with longitudinal studies.

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