Effect of Maximal Respiratory Manoeuvres on Bronchial Sensitivity of Asthmatic Patients as Compared to Normal People

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British Medical Journal, 1975, **1**, 123-125

Summary

Cumulative dose-response curves to carbachol given by aerosol were established using plethysmographic measurements of specific airways resistance (SRaw) in 10 patients with asthma and five healthy subjects. Two experiments were performed—a control test and one in which maximal respiratory manoeuvres (MRM) (two maximal inspirations and two maximal expirations) were made before each carbachol inhalation. MRM did not modify the dose-response curves in the normal subjects. In the patients these manoeuvres enhanced the bronchoconstrictor effect of carbachol: curves were shifted to the left and the mean dose of carbachol producing a twofold increase in initial SRaw was decreased from 0·373 mg to 0·189 mg ($P < 0.001$). Bronchial provocation tests using methods which require MRM—for example, forced expiratory volume at one second—could overestimate the bronchial sensitivity of patients with asthma.

Introduction

Since the early works of Dautrebande and Philippot (1941), Tiffeneau and Beauvallet (1945), and Curry (1947) bronchial provocation tests have been commonly used to assess the bronchial sensitivity of patients with asthma. In such tests the effects of graded doses of a bronchoconstrictor agent given by aerosol are measured until clear evidence of bronchial obstruction is obtained.

The most widely used methods for the evaluation of bronchial obstruction are forced expiratory flow measurements—forced expiratory volume at one second (FEV_1), maximal mid-expiratory flow rate, peak expiratory flow rate, and partial or maximal flow-volume curves—which require a maximal respiratory manoeuvre (MRM)—that is, inspiration to total lung capacity (TLC) and expiration from TLC to residual volume (RV). Since these manoeuvres produce acute changes in airway geometry (stretching during inspiration, compression during expiration) we considered the possibility that they may subsequently change airway sensitivity to inhaled bronchoconstrictor agents. We report here the effects of MRM on the bronchial sensitivity of asthmatic patients to inhaled carbachol.

Subjects and Methods

Five normal adults with no history or signs of chest disease or allergy and 10 patients with asthma volunteered for the study (see table). The patients were studied during symptom-free periods and received no symptomatic medication for at least 24 hours beforehand. None of these subjects was undergoing long-term steroid therapy.

Specific airways resistance (SRaw), which is the airways resistance corrected for lung volume (Guyatt *et al.*, 1970), was measured in a whole-body plethysmograph at a thoracic gas volume close to functional residual capacity using the panting technique (Dubois *et al.*, 1956).

Each subject served as his own control and was tested according to two different randomized protocols on two different days between 2 and 5 p.m., provided that the initial values of SRaw were comparable.

CONTROL EXPERIMENT

After measurement of the basal SRaw value (mean of five determinations) a dose-response curve was established using a nebulized solution of carbachol (Merck) in saline of 0·1% (w/v) for the asthmatic patients and 1% (w/v) for the normal subjects. An aerosolizer (Aerosolan Gauthier, particle size 0·1-5 μm) delivering 0·232 mg or 0·0232 mg of carbachol base per litre of air (for the 1% and the 0·1% solutions respectively) was used to fill a spirometer bell with fresh carbachol aerosol, and a two-way valve allowed inspiration from the spirometer and expiration into the room. Each subject was instructed to make from one to five inspirations of a fixed volume of aerosol (860 ml) and to hold his breath for four seconds after each inspiration to ensure a large particle retention. The carbachol inhalation of one or more 860-ml volumes represented a quantity of carbachol base varying from 0·02 to 0·1 mg or from 0·2 to 1·0 mg according to the solution used. After each carbachol inhalation SRaw was measured (mean of three determinations). The whole sequence —filling the spirometer with fresh aerosol, carbachol inhalation, and SRaw determinations—lasted about three or four minutes and was repeated until a twofold increase of initial SRaw was obtained. This procedure yielded a gradual increase of SRaw and the observer could easily modulate the intensity of the bronchial response by adjusting the magnitude of the carbachol inhalation.

The dose response curve was considered as being of the cumulative type (Van Rossum, 1963) since the progressive increase of SRaw with increasing doses was not interrupted by allowing a return to baseline values between each carbachol inhalation and carbachol is not metabolized by acetylcholinesterase. The SRaw increase recorded after several carbachol inhalations was considered to be due to the addition of the accumulated responses.

In some subjects control dose-response curves were performed on several occasions to assess the reproducibility of the inhalation method.

MRM EXPERIMENT

The second test was conducted in the same way as the control experiment except that each carbachol inhalation was preceded by MRM, performed as follows: forced expiration to RV, deep inspiration to TLC, forced expiration to RV, deep inspiration to TLC, and a return to functional residual capacity. The subject breathed normally for a few seconds and the carbachol

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Physical and Clinical Characteristics and One-second Forced Expiratory Volume (FEV_1) and Vital Capacity of Subjects

Case No.	Age (Yrs) and Sex	Duration of Asthma (Yrs)	Type of Asthma	Smoking History (Cigarettes/day)	FEV_1 (% of Predicted)	Vital Capacity (% of Predicted)	Mean Dose of Carbachol causing Twofold Increase in SRaw (mg)	
							Control Test	MRM Test
				Asthmatic Patients				
1	60 M.	20	Extrinsic (grain mill dust)	7	100	90	0·24	0·14
2	25 F.	3	Intrinsic	0	125	108	0·35	0·29
3	3 M.	3	Extrinsic (house dust)	0	80	83	0·20	0·08
4	29 M.	6	Extrinsic (house dust)	20	83	95	0·26	0·08
5	21 M.	9	Extrinsic (house dust)	20	93	104	0·38	0·18
6	35 M.	4	Extrinsic (house dust)	0	91	87	0·48	0·34
7	41 F.	14	Extrinsic (grass pollen)	0	85	93	0·33	0·18
8	25 F.	2	Extrinsic (house dust)	0	124	116	0·37	0·14
9	18 F.	1	Intrinsic	20	88	85	0·64	0·28
10	18 M.	6	Extrinsic (house dust)	10	103	96	0·48	0·18
				Normal Subjects				
11	40 M.			0	118	128	2·4	2·5
12	26 M.			10	103	109	3·8	3·8
13	20 F.			0	114	100	2·0	2·0
14	26 M.			0	105	110	1·8	2·0
15	28 F.			10	100	110	4·8	4·8

inhalation was then started. This sequence of expirations and inspirations mimics the procedure used when measuring partial or maximal flow-volume curves (Bouhuys *et al.*, 1969). MRM were performed while filling the spirometer bell with fresh aerosol so that the duration of the total sequence of events was about the same as in the control test. There was an interval of about one to one and a half minutes between the MRM and the first measurement of SRaw. For each subject the carbachol inhalations were similar in both experiments so that any difference in the carbachol response was due to MRM. To quantify the effect of MRM the doses of carbachol causing a twofold increase of SRaw in both tests were calculated from the cumulative dose-response curves and compared. When there were several control dose-response curves the value shown represents a mean value. At the beginning of the test MRM were performed after initial SRaw measurements were taken and a new SRaw determination was made to evaluate the effect of this manoeuvre on the resting values.

Results

In normal subjects MRM caused only inconsistent and minor changes of basal SRaw, but in the patients some increase of SRaw was usually observed (fig. 1). After MRM the thoracic gas volume was not modified so that changes in SRaw could not be attributed to changes in lung volume. When more than 3 mg of carbachol was inhaled several side effects (sweating, salivation, blurred vision) appeared in some patients.

In spite of individual variations MRM increased the bronchial sensitivity of all asthmatic patients tested (see table and fig. 1). Dose-response curves were shifted to the left and the mean dose (± S.E.) of carbachol producing a twofold increase of SRaw decreased from 0·373 ± 0·041 mg in control experiments to 0·189 ± 0·046 mg in experiments with MRM, the difference being highly significant ($P < 0·001$) when analysed using Student's paired *t* test.

In contrast MRM did not modify the bronchial sensitivity of normal subjects (fig. 2). The figs. also show that control determinations of bronchial sensitivity with this inhalation technique were highly reproducible. As expected asthmatic patients reacted to much smaller quantities of carbachol than normal subjects.

Discussion

Our main finding was the significant increase of bronchial sensitivity of asthmatic patients to a bronchoconstrictor agent, carbachol, when the inhalation of this drug was preceded by MRM. These manoeuvres are required for routine methods of measuring the forced expiratory flow.

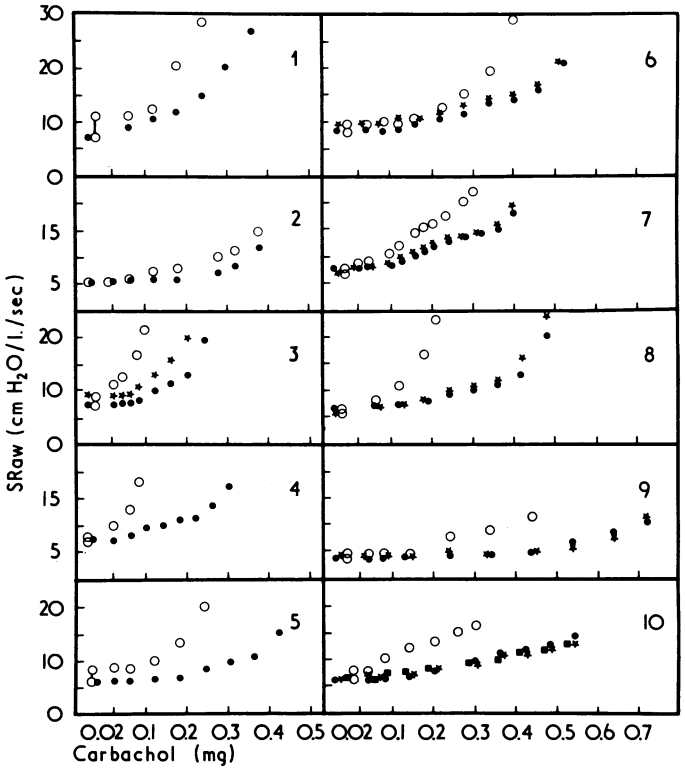

FIG. 1—Effect of maximal respiratory manoevres (MRM) on bronchial sensitivity to carbachol aerosol in 10 asthmatic patients. Case numbers are shown. Solid lines indicate changes of basal SRaw caused by MRM alone. ● = Determinations on control experiment. ★ = Repeat control determinations. ○ = Determinations on MRM experiment.

MRM could increase the bronchoconstrictor effect of carbachol in several ways. It could cause modifications of pulmonary mechanics—for example, elastic recoil—changes in aerosol distribution, or changes in Po_2/Pco_2 levels or modifications of the bronchomotor mechanisms themselves. The first three hypotheses are unlikely to be correct since these changes would also be observed in normal people, but differences could exist between normal subjects and asthmatic patients.

The fourth hypothesis is more appealing since it is commonly known that patients with asthma have abnormal airway function, as shown by the hyper-reactivity of their airways to various stimuli. MRM could enhance this hyper-reactivity (*a*) by a direct action on the muscle if the stretching and shortening of the airways, due to MRM, disturb the subtle mechanisms of smooth muscle contraction and relaxation or make the specific cholinergic receptors of the respiratory smooth muscle more sensitive to

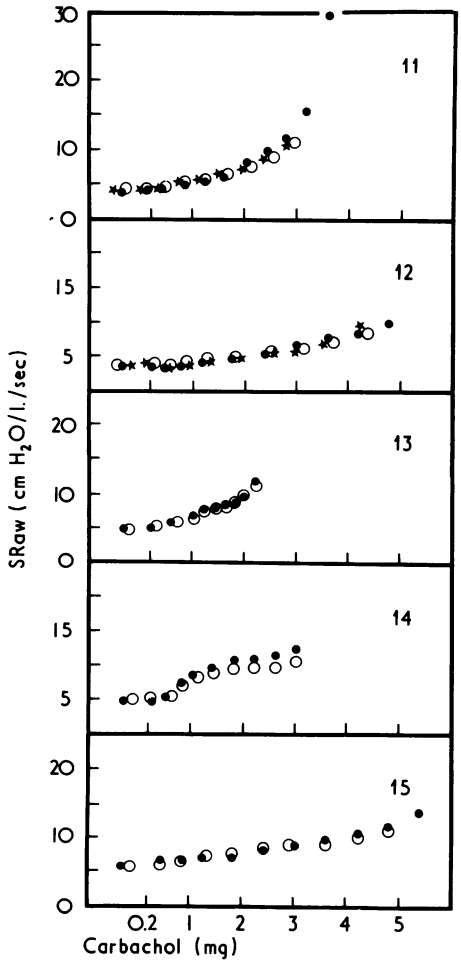

FIG. 2—Effect of maximal respiratory manoevres (MRM) on bronchial sensitivity to carbachol aerosol in five normal subjects. Case numbers are shown. ● = Determinations on control experiment. ★ = Repeat control determinations. ○ = Determinations on MRM experiment.

carbachol; (*b*) by releasing a prostaglandin since prostaglandins of the E and F series are released by mechanical stimuli (Piper and Vane, 1971) and distension (Berry *et al.*, 1971; Said *et al.*, 1972) of the lungs. Prostaglandin $F_{2\alpha}$ release could potentiate the carbachol bronchoconstrictor effect since asthmatic patients are more sensitive to this prostaglandin (Mathé *et al.*, 1973); or (*c*) by stimulating the lung irritant receptors, which cause a vagally mediated bronchoconstriction (Widdicombe, 1963). In this condition the increased vagal tone would make the airways more sensitive to bronchoconstrictor agents (Douglas *et al.*, 1973).

The last possibility is supported by the observation of Simonsson *et al.* (1967) that deep inspiration (and also deep expiration) causes bronchoconstriction in asthmatic patients, which is prevented by atropine, whereas deep inspiration causes a slight bronchodilatation in normal subjects at rest (Vincent *et al.*, 1970) and after induced bronchoconstriction (Nadel and Tierney, 1961). These findings could help to explain the difference we observed between normal subjects and asthmatic patients.

The practical consequences of these findings must be considered since lung-function tests used to determine the bronchial sensitivity of asthmatic patients compared to controls usually involve such a sequence of MRM and inhalations of a bronchoconstrictor agent. This method probably leads to overestimation of the bronchial sensitivity of patients with asthma. Furthermore, since MRM does not equally enhance the bronchial sensitivity of all asthmatic patients the comparison of bronchial sensitivity between patients would also be biased. Thus accurate comparisons must be performed using a technique such as the measurement of airway resistance with a body plethysmograph, which does not require MRM.

Our results suggest also that situations in which spontaneous MRM occur—for example, hyperventilation due to exercise—could precipitate an attack of asthma.

We thank the Institut National de la Santé et de la Recherche Médicale for financial support and Dr. A. J. Lewis for his efforts to improve the language of our paper.

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