

A Non-Pharmacologic Approach to the Treatment of Exercise-Induced Bronchospasm

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Received October 9, 1980

We investigated the effects of breathing air warmed and fully saturated to body temperature (AWS) before, during, and after exercise in asthmatic subjects. Airway responses to submaximal exercise on a cycloergometer were measured on four separate days in 14 asthmatic volunteers. On day 1 the subjects exercised breathing ambient air (AA). On the subsequent three days exercise was performed with the subjects breathing AWS, (1) for five minutes preceding, (2) during, and (3) for five minutes following exercise. We showed complete protection against EIB by AWS during exercise, but no protection by AWS before or after exercise. On two subsequent days we examined the effects of partially warming and humidifying the subjects' inspired air by having them wear a mask during exercise. We found that with such protection bronchospasm was significantly but not completely blunted. We conclude that the physiologic changes initiated during exercise can be prevented by breathing AWS during exercise, but are not by AWS inhaled before or after exercise. Furthermore, these studies demonstrate the possibility of using masks as a non-pharmacologic means of controlling EIB.

INTRODUCTION

Physical exertion is known to precipitate clinical bronchospasm in many asthmatics [1-3]. Airway obstruction occurs within a few minutes after cessation of exercise and gradually subsides after several hours. It is well recognized that asthmatics who demonstrate exercise-induced bronchospasm (EIB) have more severe attacks in cold weather, and Strauss et al. [4] have recently shown that the bronchoconstrictor effect of exertion can be markedly enhanced by having EIB susceptible patients breathe cold dry air during exercise. Deal et al. [5] have demonstrated that this phenomenon is directly related to respiratory heat exchange (RHE) in the airways of subjects with asthma, and that RHE can be directly correlated with the severity of pulmonary function deterioration following exercise.

Respiratory heat exchange (RHE) is a quantitative representation of heat flux in the tracheobronchial tree, and may be expressed by the formula:

$$RHE = \dot{V}_E [HC(T_i - T_e) + HV (WC_i - WC_e)]$$

where RHE is the respiratory heat exchange in Kcal/min; \dot{V}_E , minute ventilation in l/min (BTPS); HC, heat capacity of air (0.000304 Kcal/l per °C); T_i , inspired air temperature (°C); T_e , expired air temperature (°C); HV, latent heat of vaporization

of water (0.58 Kcal/g); WC_i , water content of inspired air in MgH_2O/e ; WC_e , water content of expired air in MgH_2O/e [5].

We sought to further explore some practical implications of these relations in asthmatic subjects by increasing inspired air temperature and humidity and thereby altering RHE. We determined the influence of breathing air warmed and saturated to body temperature before, during, and after exercise in order to better understand how modifying inspired air conditions could alter EIB. We further investigated the therapeutic potential of wearing a mask during exercise as a means of partially warming and humidifying inspired air to body conditions in order to determine whether non-pharmacologic methods might be useful in the management of EIB.

SUBJECTS AND METHODS

Exercise challenge studies were performed on asthmatic subjects who were selected because of a history strongly suggestive of EIB. All the subjects were otherwise healthy non-smoking young adults aged 24.9 ± 6.8 years (mean \pm 1 SD). There were nine male and five female subjects. All had a past history of asthma as defined by the American Thoracic Society [6]. The subjects were mild asthmatics; none had ever required steroid therapy or disodium cromoglycate for control of their disease. None had been hospitalized. All subjects gave informed consent as approved by the Yale University Human Investigation Committee.

In all cases, exercise studies were performed at least twenty-four hours after cessation of a subject's usual asthma medications, and exercise challenge took place at approximately the same time of day for each individual to avoid any possible effects of diurnal variation.

Pulmonary function was assessed using partial and maximal expiratory flow volume curves. These measurements were performed using a pneumotachograph integrator system [7] and the results were recorded on an X-Y recorder (Gould Brush 500, Cincinnati, OH) with flow plotted against volume. For each test the subject inspired to approximately 70 percent of vital capacity and then exhaled forcefully to residual volume. The subject then inhaled to total lung capacity and once again forcefully exhaled to his residual volume. These maneuvers generated partial and maximal expiratory flow volume (PEFV and MEFV) curves (see Fig. 1). From these plots, the forced vital capacity (FVC), forced expired volume in one second (FEV_1),

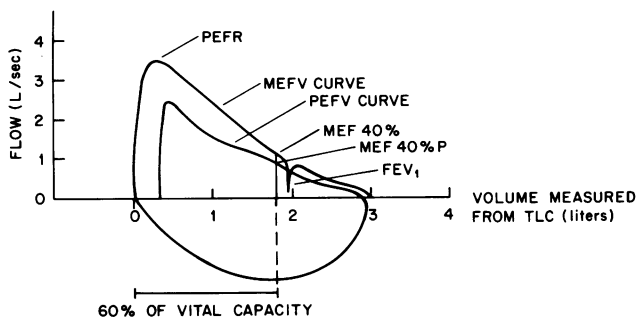


FIG. 1. Partial and maximal expiratory flow volume (PEFV and MEFV) curves. Partial and maximal flow rates are measured at a volume point which is 60 percent of the average baseline vital capacity below TLC. Forced expired volume in one second is indicated by a one second marker on the MEFV curve. TLC = Total Lung Capacity; PEFR = Peak Expiratory Flow Rate; FEV_1 = one second forced expired volume, MEF40% and MEF40%(P) = Maximal expiratory flow at 60 percent of vital capacity below TLC measured on MEFV and PEFV curves, respectively.

and peak expiratory flow rate (PEFR) as well as maximal expiratory flow rates on maximal (MEF40%) and partial (MEF40%(P)) flow volume curves at 60 percent of the control vital capacity below TLC were determined [8]. Flows were measured at this level rather than at 50 percent of VC in order to avoid the "transient" peak flow level on the partial flow volume curve.

All exercise studies were performed on a cycloergometer (Monark). Subjects underwent progressive exercise testing on their first study day to determine an exercise load that would achieve a submaximal effort as judged by a heart rate of 150 beats/minute or better. The same exercise load was used on each subsequent test day for the subjects. During these studies exercise was increased by a fixed increment of 150 Kilopond meters per minute (Kpm/min) every minute as described by Jones et al. [9]. In a previous study [10] we have shown that such a challenge elicits some degree of EIB in virtually all asthmatics tested. The subject's heart rate was measured at the end of every minute by monitoring the electrocardiographic pattern (Hewlett Packard, Model 1500B, Waltham, MA). Minute ventilation (V_E) was measured at the end of each minute by directing exhaled air through a calibrated gas meter. Inspired air was channeled through an Otis McKerrow valve (Warren E. Collins, Braintree, MA), directing room or conditioned air into the subject's airway and exhaled air through the gas meter (Fig. 2). This system was not used during the second study as the subjects were wearing masks and it was not possible to measure their minute ventilation in this fashion.

The laboratory in which the studies were performed was centrally air-conditioned and both the room temperature and humidity were kept within narrow limits: $T = 22.6 \pm 1.62^\circ\text{C}$. Relative Humidity (RH) = $37.5 \pm 4.4\%$ (mean \pm SD). These were considered our ambient air (AA) conditions.

Two series of studies were performed. In the first (Study I) we examined the effect of warming and humidifying inspired air before, during, and after exercise. Ten subjects participated. On the first day of the study, the subject exercised breathing ambient air (AA). On the subsequent three days the exercise challenge was repeated to the same work-load level. On these three days, the subjects breathed air warmed and fully saturated to body temperature (AWS) by passage through a heated cascade humidifier (Puritan Bennett, No. 008926, Kansas City, MO) filled with sterile water, and connected to the inspiratory port of the Otis-McKerrow valve (see Fig. 2).

Subjects wore a nose clip to assure that only the conditioned air, AWS or AA, was inhaled, and that the "air-conditioning" effects of nasopharynx were bypassed. Temperature was measured at the proximal opening of the valve, and the humidifier temperature setting was adjusted to maintain inspired air temperature at 37°C . On

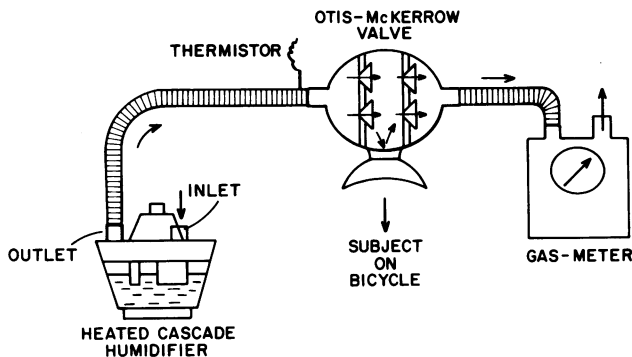


FIG. 2. Schematic representation of the system used to deliver AWS to the subjects.

each of the study days the subject inhaled modified air for five minutes before, during, and after exercise, respectively. Pulmonary function was measured prior to exercise, immediately following exercise, and six minutes following the cessation of exercise. All measurements were repeated three times at intervals of one minute and the results averaged from each of the time periods [10].

In the second series of the studies (Study II), ten subjects (refer to Table 1) were used (six of whom had participated in the initial series of studies). The study consisted of two separate days on which exercise challenge was performed. As in the first study, the initial day consisted of a submaximal exercise challenge performed on a cycloergometer, to document the degree of EIB experienced by each subject under AA conditions. This challenge differed from those of the first study in that subjects were not forced to breathe through their mouths by the use of a nose-clip during exercise. On the second day the same format was followed except that this time subjects wore a mask (3M, Micropore^{T.M.} germ and pollen mask) during the exercise period.

Following the final post-exercise measurements of pulmonary function, subjects received two inhalations from a standard nebulizer containing metaproterenol. Post bronchodilator pulmonary function was measured ten minutes following inhalation.

RESULTS

Baseline pulmonary function studies performed on the subjects in the first study day of both experiments revealed mild airway obstruction (Table 1). The average (mean \pm SD) exercise load achieved during the studies was 945 ± 147 kpm/min. Maximal heart rates and ventilations are detailed in Table 2 for individual study days and show no significant differences. Baseline pulmonary function of the initial study days was compared with baseline function of the subsequent study days (Table 3). No significant differences were demonstrated by a one-way analysis of variance ($p > 0.05$) for Study I days and by the paired *t*-test for Study II days ($p > 0.05$) [11].

Significant exercise-induced bronchospasm was demonstrated on the initial study day of both studies (refer to Table 4). In our first study, when subjects were exercised breathing air warmed to body temperature and humidified by the heated cascade humidifier, we did not observe significant post-exercise bronchospasm for the group as a whole. However, one individual did manifest a 10 percent fall in FEV₁ and two decreased their MEF40%(P) by more than 20 percent. Both of these changes were less than the corresponding decreases of the initial day. Furthermore, both individuals demonstrated a sequential decrease in flow rates following repeated forced vital capacity maneuvers (independent of exercise). It is postulated that in these two subjects the bronchospasm seen following exercise protected by AWS was a result of the multiple dynamic vital capacity measurements; such a phenomenon has been described by Orehek et al. [12]. Table 5 compares the post-exercise pulmonary function changes on the four separate test days for mean FEV₁ and MEF40%(P). As can be seen, breathing AWS offered no advantage over the baseline study when inhaled before or after exercise. Of interest is the significantly greater post-metaproterenol response observed on the second study day during which AWS was breathed during exercise.

Comparison of the initial day of the second study (no mask) to the mask day demonstrated significant but incomplete protection. This effect was noted for all functional parameters measured and is illustrated in Figs. 3 and 4 for FEV₁ and MEF40%(P), respectively. Note that metaproterenol improved post-exercise func-

TABLE 1
 Baseline Pulmonary Function Measurements (expressed as a percentage of predicted) of Subjects Studied*
 (Mean ± SD)

	Number of Subjects	Sex		Age	FVC	FEV ₁	PEFR	V̇max 50%
		M	F					
Study 1 (Cascade humidifier)	10	8	2	25.1 ± 7.9	89.5 ± 12.3	79.1 ± 18.1	78.3 ± 20.5	61.1 ± 25.2
Study 2 (mask)	10	6	4	23.0 ± 5.7	93.0 ± 13.0	78.8 ± 18.5	74.9 ± 23.3	61.4 ± 24.2

*Predicted values obtained from Higgins MW, Keller JB: Seven Measures of Ventilatory Lung Function. Amer Rev Resp Dis 108:258-272, 1973

TABLE 2
Average (Mean \pm SD) Maximal Heart Rates (HR) and Ventilation (V_E)
Achieved on Each Study Day of the Two Experiments

	Heart Rate (Beats/min)	Minute Ventilation (L/min)
<i>Study I</i> (cascade humidifier)		
Day 1 (ambient)	168.2 \pm 19.7	62.3 \pm 14.2
Day 2 (AWS during)	166.0 \pm 14.8	57.7 \pm 12.5
Day 3 (AWS after)	163.0 \pm 15.3	60.5 \pm 15.1
Day 4 (AWS before)	165.0 \pm 15.1	61.3 \pm 10.3
<i>Study II</i> (mask)		
Day 1 (No mask)	163.8 \pm 12.4	
Day 2 (mask)	166.6 \pm 12.3	

Study I: Maximal work load 960 \pm 126 Kpm/min

Study II: Maximal work load 930 \pm 171 Kpm/min

tion to better than baseline on both test days, but that the response on the mask day was greater.

Although for the group as a whole protection was only partial, in two of our subjects the protection was complete, as illustrated by the series of flow volume curves illustrated in Fig. 5.

In order to evaluate conditions within the mask we measured mask temperature by means of a thermistor probe (Diatek, San Diego, CA) secured within the mask. We also measured F_{CO_2} inside the mask using a quadrupole mass spectrometer (Centronic, Croydon, England) to continuously monitor inspired CO_2 concentration. Measurements were made in six healthy subjects both at rest and at the end of six minutes of submaximal exercise. Values for temperature and inspiratory F_{CO_2} are recorded in Table 6.

TABLE 3
Comparison of Baseline Pulmonary Function Obtained on the Initial Study Day
with Those Obtained on Subsequent Study Days
(Mean \pm SD)

Study I (cascade humidifier)	Day 1 (ambient)	Day 2	Day 3	Day 4
		(cascade humidifier during)	(cascade humidifier after)	(cascade humidifier before)
FVC (L)	4.55 \pm 1.00	4.49 \pm 1.06	4.35 \pm 1.09	4.52 \pm 1.11
FEV ₁ (L/Sec)	3.24 \pm 0.88	3.16 \pm 0.93	3.08 \pm 1.02	3.23 \pm 1.03
PEFR (L/Sec)	6.78 \pm 2.12	6.48 \pm 2.25	6.53 \pm 2.21	6.63 \pm 2.45
MEF40% (L/Sec)	2.56 \pm 1.06	2.44 \pm 1.10	2.34 \pm 1.31	2.45 \pm 1.18
MEF40%(P) (L/Sec)	2.46 \pm 1.21	2.21 \pm 1.02	2.34 \pm 1.17	2.33 \pm 1.29
Study II (mask)	Day 1 (no mask)	Day 2 (with mask)		
FVC	4.48 \pm 1.00	4.35 \pm 1.05		
FEV ₁	3.06 \pm 0.99	2.93 \pm 1.03		
PEFR	6.28 \pm 2.71	6.04 \pm 2.89		
MEF40%	2.22 \pm 0.95	2.1 \pm 1.17		
MEF40%(P)	2.19 \pm 1.10	2.08 \pm 1.27		

TABLE 4
 Exercise-Induced Bronchospasm (EIB) Demonstrated on the Initial Day of
 Each Study, Expressed as a Percentage of Baseline
 (Mean \pm SD)

	Baseline (%)	Time Following Exercise		
		0 Min.	6 Min.	20 Min.*
Study I (cascade humidifier)				
FVC	100	94.2 \pm 5.2**	92.1 \pm 7.8†	107.7 \pm 20.9
FEV ₁	100	93.1 \pm 15.5	85.6 \pm 12.4††	112.4 \pm 16.9†
PEFR	100	95.2 \pm 14.4	83.7 \pm 15.3**	109.3 \pm 13.7†
MEF40%	100	94.4 \pm 29.1	72.2 \pm 25.7**	122.6 \pm 24.5†
MEF40% (P)	100	93.1 \pm 32.6	67.5 \pm 21.5††	147.7 \pm 38.7††
Study II (mask)				
FVC	100	93.1 \pm 6.7††	91.1 \pm 9.1**	102.2 \pm 8.0
FEV ₁	100	90.0 \pm 12.4	80.6 \pm 13.6††	106.8 \pm 11.1
PEFR	100	91.5 \pm 13.7	80.0 \pm 15.5††	92.5 \pm 11.8
MEF40%	100	82.2 \pm 31.4	57.9 \pm 28.9††	119.0 \pm 25.4†
MEF40% (P)	100	71.8 \pm 38.7	49.4 \pm 25.7††	127.7 \pm 27.5**

*Ten minutes following inhalation of 2 metered doses of metaproterenol

† $p < 0.05$

** $p < 0.01$

DISCUSSION

We have demonstrated that breathing air warmed to body temperature and fully saturated can considerably modify post-exercise bronchospasm in susceptible individuals. The protection afforded by breathing AWS during exercise supports the hypothesis that respiratory heat exchange (RHE) acts as the major stimulus causing EIB [5,13,14].

Measurements of EIB, under different environmental conditions, as a function of the fall in FEV₁ (% Δ FEV₁) has shown that in mild, relatively stable asthmatics % Δ FEV₁ can be related by a linear regression to RHE [15]. Similarly manipulation of environmental condition and eucapnic hyperventilation have been shown to lead to a degree of EIB predicted by the above regression [16]. Such findings strongly suggest that RHE is the initiating mechanism for constriction following exercise.

Respiratory heat exchange has been characterized by the formula: $RHE = \dot{V}_E [HC(T_i - T_e) + HV(W_{Ci} - W_{Ce})]$ where RHE is measured in Kcal/min; \dot{V}_E is the minute ventilation of the subject measured in e/min , BTPS; HC is the heat capacity of air = 0.00034 Kcal/ $e \cdot C^\circ$; T_i and T_e the inspired and expired air temperature in $^\circ C$; HV the heat of vaporization of water = 0.58 Kcal/g; and W_{Ci} and W_{Ce} the inspired and expired water content of air in $\text{mgH}_2\text{O}/e$ air (M). Since HC and HV are constants and T_e and W_{Ce} are generally assumed to reflect BTPS conditions, three variables influence the magnitude of RHE: namely \dot{V}_E , T_i , and W_{Ci} . Since \dot{V}_E is a function of the level of exercise achieved, this variable cannot readily be influenced. The two environmental conditions, on the other hand, T_i and W_{Ci} , can be readily manipulated by simple means as we have shown in our study. The finding that AWS inhaled following exercise has no effect on EIB is not surprising. Many bronchodilating agents, namely the beta agonists, methylxanthines, and carbon dioxide [17], have been demonstrated to reverse EIB following its onset. These agents are felt to work

TABLE 5
 Changes in FEV_{1,0} and MEF40%(P) Post-exercise, as a Percentage of Baseline Function on the Four Study Days
 (Mean ± SE)

	Time after Exercise	Day 1 (Ambient)	Day 2 (AWS during)	Day 3 (AWS after)	Day 4 (AWS before)
FEV _{1,0}	0 minutes	-6.9 ± 4.90	+6.7 ± 2.12*	-	-6.1 ± 4.87
	6 minutes	-14.4 ± 3.92	+1.8 ± 2.06**	-14.2 ± 5.88	-13.5 ± 5.50
	After				
MEF40%(P)	Metaproterenol	+12.4 ± 5.34	+13 ± 2.78	+11.1 ± 3.57	+10.6 ± 3.79
	0 minutes	-6.9 ± 10.30	+31.1 ± 12.00†	-	-0.5 ± 9.87
	6 minutes	-32.5 ± 6.80	+0.4 ± 10.72**	-36.8 ± 13.22	-27.5 ± 9.31
	After				
	Metaproterenol	+47.7 ± 12.23	+58.6 ± 11.43	+41.8 ± 16.55	+41.9 ± 8.64

*p < 0.05

**p < 0.005

†p < 0.01

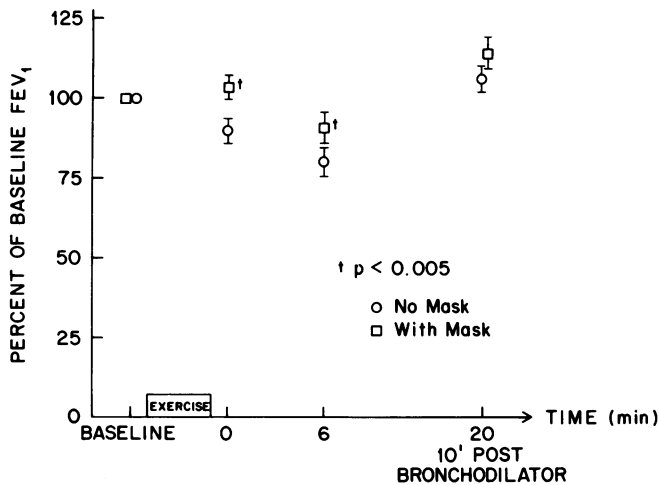


FIG. 3. Post-exercise FEV₁ changes for the group measured on the two days of Study II. (Mean ± SE).

by direct bronchodilation and not to influence the mechanism underlying EIB. AWS has no such bronchodilating properties. If one postulates that the bronchoconstrictor mechanisms triggered by exercise are actively initiated only during exercise, and that AWS blocks this mechanism, its failure to alter post-exertional bronchospasm once initiated is readily understood. The fact that EIB may only become apparent several minutes following the cessation of exercise has been attributed to the fact that there is endogenous release of catecholamines during and immediately after exercise suppressing bronchospasm. Hence, the onset of bronchoconstrictor forces probably occurs during exercise. We had initially postulated that humidification of inspired air prior to exercise might alter EIB by somehow insulating the surface coat of the airway but this did not, in fact, prove to be the case.

A practical implication of these findings is that the contribution of environmental conditions must be assessed in evaluating any form of induced bronchospasm. In

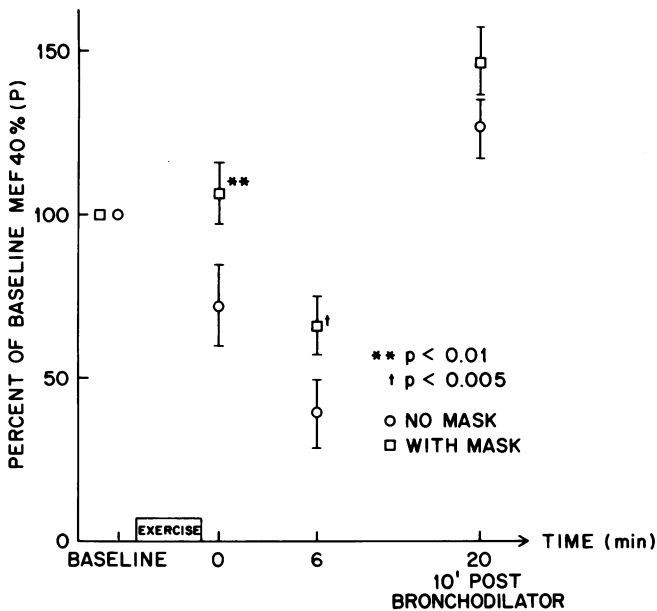


FIG. 4. Post exercise MEF40%(P) changes for the group measured on the two days of Study II (Mean ± SE).

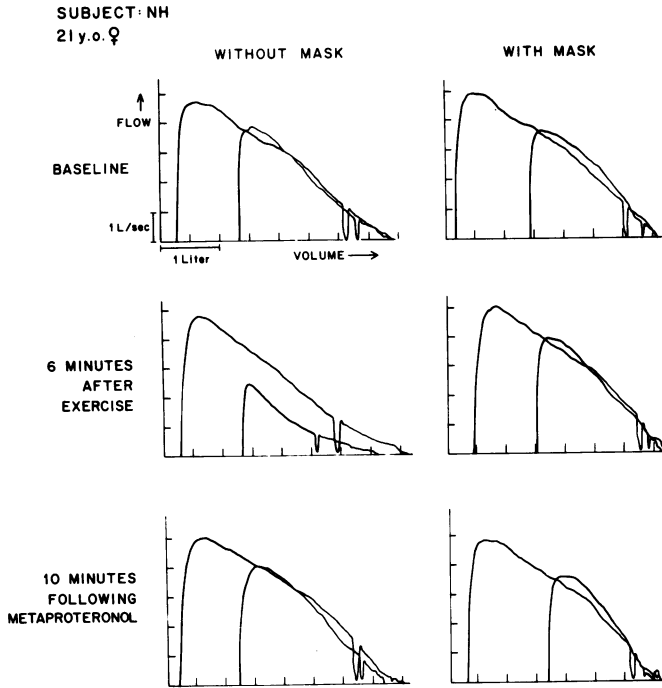


FIG. 5. Sequential changes in subject NH on the two days of Study II demonstrating complete protection against EIB.

particular, the temperature and humidity of ambient air may modify EIB responses or for that matter any challenge in which there is interaction between RHE and other airway irritants. Such considerations may be important in comparing the interactions of inhalational challenges resulting in small differences; for example, those seen with ambient levels of air pollutants, under different conditions of temperature and humidity.

The second part of this study, which was suggested by the initial results, was designed to investigate the usefulness of wearing a simple mask as a potential means for the prevention of EIB. All of the subjects tested noted that air in the mask was warm and humid but not unpleasant. Wearing the mask during exercise was well

TABLE 6
Conditions Inside Test Mask Measured in Six Healthy Subjects at Rest and during Exercise

Subject	Temperature (°C)		Inspiratory F_{CO_2} (%)	
	Rest	Exercise	Rest	Exercise
ML	32.6	32.9	0.6	0.8
EM	32.2	32.2	0.2	0.2
EK	33.6	33.6	0.3	0.4
CS	33.3	33.3	0.3	0.6
BM	34.0	34.0	0.5	0.6
NS	32.7	31.8	0.3	0.5
\bar{X}	33.1	33.0	0.37	0.52
SD	0.68	0.84	0.15	0.20

tolerated, and the subjective impressions of our asthmatic group were that bronchospasm was considerably less following exercise when a mask was worn. These impressions were confirmed by the objective findings of pulmonary function testing. The data described showed a significant reduction in the degree of post-exercise airway obstruction in all flow parameters when the mask was used during exercise, and in some subjects this protection was complete (Fig. 5). The possibility that the differences in RHE provided by the mask might be due to differences in \dot{V}_E on the two study days seems unlikely in view of the relative constancy of this variable in Study I (Table 2).

Although it was our hypothesis that the protective effect of wearing a mask was due primarily to the increased temperature and humidity of inspired air, the addition of anatomic dead space within the mask raised the possibility that increased inspired F_{CO_2} might account for the protective effect seen. Previous studies have shown that the inhalation of high concentrations of CO_2 (6–8 percent) can, in fact, prevent EIB if given during exercise [2]. Our measurements showed a residual F_{CO_2} of only 0.8 percent in the mask after exhalation. This concentration would not be sufficient to cause bronchodilation of prophylactic value.

The fundamental mechanisms involved in EIB remain unknown. Two general bronchoconstrictor mechanisms which have been suggested are autonomic nervous system pathways [18,19,20] and the release of mediators from airway-associated mast cells [3,21,22]. However, studies refuting [15,23,24] these mechanisms as the sole of mixed causes of EIB offer many contradictions which await further clarification. Nevertheless, agents known to modify cholinergic [1,15,20] as well as mediator-induced bronchospasm [1,25,26] have been used to successfully treat EIB. Such agents unfortunately may be expensive or accompanied by undesirable side effects. That therapeutic modalities unrelated to the alteration of the pharmacologic effects of mediators or the cholinergic nervous system may be of value has been previously suggested by the work of McNally et al., who have shown the therapeutic effect of oropharyngeal anesthesia in EIB [18] and the work of Shturman-Ellstein et al. [27] who have demonstrated the beneficial effect of nasal breathing in EIB. These results imply that EIB may be modified at its earliest stages before nervous reflexes or endogenous chemical agents are activated. Our study confirms the value of this type of approach and suggests a practical method for treating EIB.

The practical implications of this study suggest that further protection against EIB might be achieved by using a mask that optimized the warmth and humidity of inspired air. The mask used was not designed for this purpose and, in fact, contained features that made it less than desirable. For example, the dead space was small and prevented any significant reservoir of moist warm air. The use of such masks under subfreezing conditions must also be studied as their usefulness may be limited by the accumulation of ice on the surface of the mask. Further studies with masks specifically designed for this problem appear warranted.

Our studies have confirmed the central role of heat exchange in EIB. Warming and humidifying inspired air before and after exercise had no effect on the bronchospasm following exercise; however, this environmental modification performed during exercise completely abolished EIB. Based on these concepts we have demonstrated a practical and simple means of altering respiratory heat exchange (RHE) and thereby blunting EIB by the use of a simple mask. These observations suggest an adjunctive, non-pharmacologic approach to the treatment of some forms of asthma, involving respiratory heat loss.

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