Influence of Heat and Humidity on the Airway Obstruction Induced by Exercise in Asthma

RICHARD H. STRAUSS, E. R. MCFADDEN, JR., R. H. INGRAM, JR., E. CHANDLER DEAL, JR., and JAMES J. JAEGER with the technical assistance of DAVID STEARNS, *Departments of Medicine of Peter Bent Brigham Hospital and Harvard Medical School, Boston, Massachusetts 02115 and U. S. Army Research Institute of Environmental Medicine, Natick, Massachusetts 01760*

ABSTRACT We examined the degree of airway obstruction that developed in eight asthmatics who exercised while breathing air under four conditions: (*a*) ambient room temperature and water content; (*b*) body temperature and ambient water content; (*c*) ambient room temperature fully saturated; and (*d*) body temperature fully saturated. These test conditions were performed in random order. Multiple aspects of pulmonary mechanics were measured before and 5 min after exercise. When air at ambient conditions was inhaled, the expected airway obstruction developed after exercise, and all variables changed significantly from their pre-challenge values. Heating the air to body temperature did not influence this response. Increasing the humidity at ambient temperatures significantly blunted the response, and by inhaling body temperature, fully saturated air completely prevented it from occurring. Thus, the water content of inspired air is an important variable in the development of exercise-induced asthma.

INTRODUCTION

It is a well-recognized clinical phenomenon that asthmatic individuals complain that exposure to various weather extremes, such as cold or high humidity, will often cause acute exacerbations of their disease. Although there is little objective evidence of support such associations, they are so ingrained that it is widely believed that living in a warm, dry climate will ameliorate the symptoms of this illness. In the course of investigating the effects of climatic conditions on airway reactivity in asthmatics, we have been able to demonstrate that, at least, part of these complaints have a basis in fact. When asthmatics were made to exercise while breathing subfreezing air, we found that the magnitude of their postexertional airway obstruction was markedly accentuated (1). Inasmuch as air at sub-zero temperatures contains virtually no water, our findings raised the possibility that this synergism between exercise and cold air in asthmatics might be due to some sort of defect which interferes with their ability to heat and humidify air completely during inspiration. If this were so, then preconditioning of the inspirate during exercise might possibly modify the magnitude of the subsequent airway obstruction and thereby give some insights into the mechanisms underlying exercise-induced asthma. Our results form the basis of this report.

METHODS

Eight atopic individuals, one man and seven women, with reproducible exercise-induced asthma previously documented in our laboratory, served as subjects for this investigation. Their mean age was 22.9±2.0 yr SD, and all met the American Thoracic Society's definition of asthma (2). All refrained from taking any medication for at least 12 h before any study day. None had used glucocorticoids or cromolyn sodium for at least 1 mo before these studies. Informed consent was obtained from each participant.

We measured airway resistance and total lung capacity with its subdivisions in a variable pressure plethysmograph that was serially interfaced to an analog recorder (Electronics for Medicine, White Plains, N. Y.) and a minicomputer (Lab 8E, Digital Equipment Corp. Marlboro, Mass.) (3, 4). Resistance was converted to its reciprocal, conductance, and expressed as a conductance volume ratio termed specific conductance (SG_{aw})[1] (5). Four to five measurements of each variable were

The views of the authors do not purport to reflect the positions of the Department of the Army or the Department of Defense.

Dr. McFadden is the recipient of Research Career Development Award HL 00013 from the National Heart, Lung, and Blood Institute of the National Institutes of Health.

Received for publication 1 August 1977 and in revised form 28 September 1977.

[1] *Abbreviations used in this paper:* BTPS, body temperature and pressure saturated with water; f, respiratory frequency; FEV_1, 1-s forced expiratory volume; HR, heart rate; MMF, maximum mid-expiratory flow rate; RV, residual volume; SG_{aw}, specific conductance; VE, minute ventilation; VT, tidal volume; WC, water content.

obtained, and the mean was computed. These data were considered acceptable if their coefficients of variation were 5% or less. Maximum forced exhalations were then performed in triplicate using a waterless spirometer (Electro Med model 780, Seale Cardio-Pulmonary, G. D. Seale & Co., Houston, Texas). 1-s forced expiratory volumes (FEV_1) and maximum mid-expiratory flow rates (MMF) were computed by standard techniques. The best effort, as defined by the curve with the largest forced vital capacity and FEV_1, was used for analysis.

Inspired air was conditioned by having the subjects breathe through a heat exchanger which was kept either at ambient room or body temperatures. The exchanger consisted of a heavily insulated, 76-cm-long copper tube with an internal diameter of 6.5 cm, equipped with a 10.7-cm (ID) one-way valve on the inspiratory port. In the body temperature experiments, water maintained at 37°C in a bath was circulated by pump through copper coils around the walls of the exchanger. Inspired air temperatures in all experiments were continuously recorded by a thermocouple situated in the airstream within the exchanger and located 10 cm upstream from the mouth. Expired gas was directed away from the exchanger through another one-way valve into a Tissot spirometer so that tidal volume (V_T), respiratory frequency (f), and minute ventilation ($\dot{V}_E$) could be continuously recorded. Heart rate was also monitored continuously.

The water content of the inspired air was brought to full saturation by forcing room air, with the aid of a blower, into a copper manifold (3.5 cm ID) that was perforated with multiple small holes, and was immersed in a separate water bath maintained at 50 or 29°C for the body and room temperature experiments, respectively. The incoming air then bubbled through the water where it was heated and fully humidified. It was then collected in a 25-liter meteorological balloon which was in series with the one-way valve on the inspiratory port of the exchanger. While in the balloon, the air was permitted to cool to either 41 or 27°C depending upon the experiment, so as to permit excess moisture to "rain out". As the air entered the exchanger, it then cooled further to either room or body temperature as determined by the exchanger settings, but it maintained its saturation of 100%. Adjusting the blower speed and the amount of filling of the balloon allowed us to control the rate of cooling and still provide sufficient conditioned air to meet the ventilatory demands of the exercising subjects. A thermocouple measured the temperature of the air leaving the balloon. During experiments that employed ambient room humidity, the bubble humidifier was disconnected from the exchanger.

The water content of the air leaving the mouthpiece of the exchanger was verified by sampling the airstream during simulated ventilations of up to 150 liters/min at both body and ambient temperatures. Water content of the air was determined by drawing a known volume of air through glass drying tubes containing anhydrous calcium sulfate (W. A. Hammond Drierite Co., Xenia, Ohio). From the change in weight of the drying tube and the volume of air sampled, water content was expressed as mg H_2O/liter air. The ambient temperature and humidity of the room were measured with a standard mercury thermometer and a hygroscopic membrane hygrometer (Bacharach Instrument Co., Pittsburgh, Pa.), respectively. The accuracy of the latter was also verified by sampling room air and determining its water content by standard physical means as above.

In the first series of experiments we investigated the effects of breathing air at body temperature with various humidities on the pulmonary mechanical response to exercise. This was accomplished by having the subjects perform three bouts of exhausting leg work on a cycle ergometer while breathing air at ambient temperature and water content, body temperature and ambient water content, or body temperature fully saturated, in a random fashion. The ambient condition experiment was used as a control. Each type of air was breathed for 4 min before, during, and for 4 min after exercise.

Upon completion of each exercise period, the subjects were allowed to rest for at least 1.5 h while their pulmonary function returned to pre-exercise levels. When this had occurred, the exercise was then repeated using identical work loads, revolutions per minute, and durations for each individual. The mean workload was 806±178 kpm SD, and the mean duration of exercise was 3.13±0.54 min SD.

Exhausting leg work was used as the provocational stimulus because it was technically easier to have the subjects breathe through the exchanger from a fixed seated position. Previous experience with this form of maximum work had demonstrated that it is a highly effective and reproducible means of inducing bronchospasm (1, 6, 7). Similarly, the duration of work, the interval between studies, and the number of studies that could be performed within a day had all been previously verified as being appropriate (1, 6–9).

Pulmonary mechanics were measured before and 5 min after cessation of work. Again, prior experiments demonstrated that this time sequence would coincide with the maximal response (1, 6–9). As indicated, ventilations and heart rates were measured continuously before and during exercise. The data from the last minute of the rest and exercise periods were analyzed.

To isolate the effects of humidity per se, a second set of experiments was performed on a different day. In this study, air of ambient temperature was completely humidified, and the response compared to that seen with ambient temperature and water content. As before, the experimental sequence was randomized. The work loads were identical to those used on the first day and were kept constant for each study for each subject. Pulmonary mechanics, ventilation, and heart rates were measured as previously described.

To determine if the very act of inhaling air at different temperatures and humidity was altering lung function before the application of the exercise stimulus, we measured peak flow rates while our subjects were breathing each of the test gases. This was achieved by placing a Wright peak flow meter (Puritan Bennett Corporation, Kansas City, Mo.) in series with the expiratory port of the exchanger. This technique was employed because it allowed us to make measurements of mechanics without interfering with our assessments of resting ventilation and heart rates. Data were obtained immediately after the subject went on the mouthpiece and then serially at 1-min intervals for the 4 min before exercise commenced.

The statistical analysis used in this study consisted of paired *t* tests and both one- and two-factor analyses of variance.

RESULTS

These studies were performed in an air-conditioned room at sea level where the ambient temperatures and relative humidities varied between 22 and 25°C, and 23 and 53%, respectively. In that relative humidity is defined as the amount of water present as a proportion of the quantity that the air can hold, and in that the latter varies with temperature, a given water content can be associated with different relative humidities. For example, if the ambient water content were 10 mg H_2O/liter air at a temperature of 25°C, this would correspond to a relative humidity of 43%. However, if this air were heated to 37°, relative humidity would fall

to 23%, because the amount of water the air could contain at 37° has risen by 21 mg/liter. Consequently, to avoid confusion, this report will present all saturation data in terms of absolute water content in milligrams of water per liter of air.

The validation data for the measurement of water content are contained in Fig. 1. The data were obtained with the bubble humidifier at ventilations ranging from 80 to 150 liter/min and at air temperatures of 24 and 37°C within the heat exchanger. Panel A demonstrates that there were no significant differences between the expected water contents and those physically measured, and panel B shows that water content remained constant even at ventilations greatly in excess of those seen in this study.

The effects of exercise on pulmonary mechanics while breathing air at different temperatures and humidities are shown in Tables I—IV and Figs. 2 and 3. In the control experiment, the mean ambient temperature was 23.7±0.9°C SD, and the water content ranged from 5.3 to 9.3 mg/liter of air (mean = 7.6±1.6 mg H_2O/liter air). During exercise, $\dot{V}E$ was 71.3±9.0 liters/min, and the mean heart rate was 165±11 beats/min. As can be seen in Table I, significant airway obstruction developed. Specific conductance fell an average of 58% from its base-line value, and FEV_1 and MMF decreased 24 and 20%, respectively, from theirs. Residual volume rose 61%. Heating the inspired air to 37.4±0.2°C, but leaving water content at ambient values (8.7±0.8 mg H_2O/liter air), had no effect upon the response (Table II, Figs. 2 and 3). Comparisons of absolute values for the base line and response data with those in the control experiment by a two-factor analysis of variance did not reveal any differences in these two studies ($F < 1.0$ for every variable).

When the air was fully humidified (20.4±0.4 mg H_2O/liter air) at ambient temperatures (22.9±0.14°C), airway obstruction still developed in that all variables changed significantly from control (Table III), but the magnitude of the response was significantly less than it was in the previous two experiments ($P < 0.01$ for each variable) (Figs. 2 and 3). Specific conductance now fell only 23% whereas FEV_1 and MMF changed 9 and 18%, respectively. Residual volume was only 23% greater than its pre-exercise value. Having the subjects inspire air at body temperature (37.1±0.5°C) with full saturation (44.1±1.0 mg H_2O/liter air) abolished the response in that there was no significant decrement in lung function after exercise (Table IV). In point of fact, the spirometric variables actually improved over pre-exercise values, MMF significantly so. Residual volume rose 16%, but these changes are no greater than those previously reported to occur in normal subjects after strenuous exertion (8, 10). This response was significantly different from the previous three experiments at the 0.01 level or less for all aspects of mechanical lung function except RV. No differences were found between experiments 3 and 4 (ambient

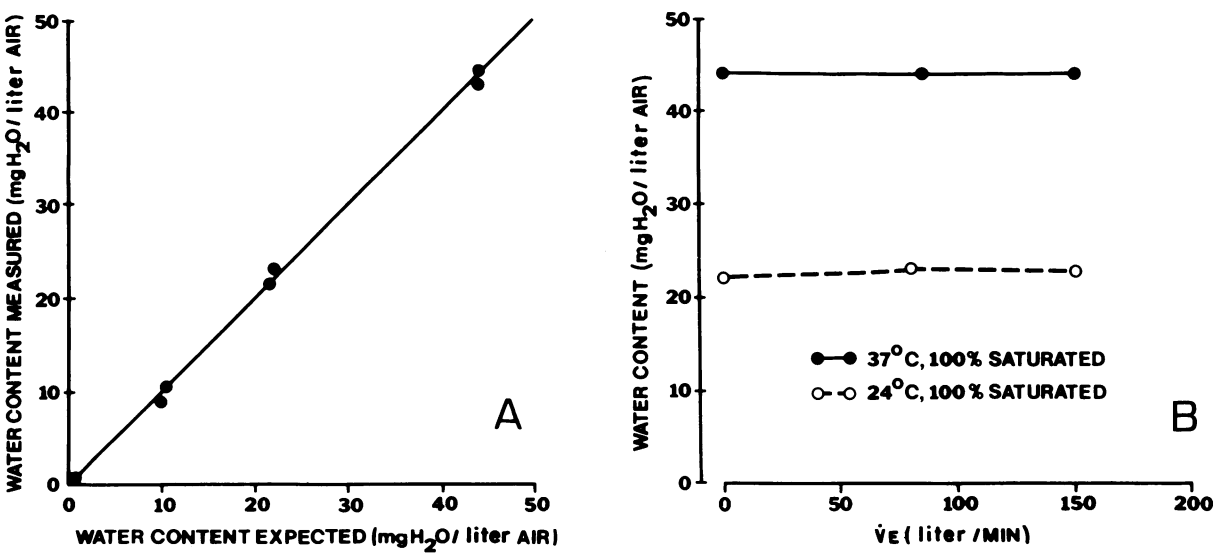

FIGURE 1 Validation experiments for the use of the Bubble Humidifier. (A) The graph plots the expected water content of the inspired air (derived from calculations using air temperature and relative humidity) on the horizontal axis vs. measured contents at the mouthpiece of the exchanger with the humidifier in action on the vertical scale. The horizontal line is the line of identity. Each data point represents a separate determination. The zero point was obtained with compressed air. (B) The graph shows the stability of the inspired water content at various airflows through the humidifier-heat exchanger circuit. The data points represent the mean of several determinations.

TABLE I

Effects of Exercise on Pulmonary Mechanics While Breathing Air at Ambient Temperature and Humidity

Subject	T	WC	$\dot{V}_E$	HR	SG_{aw}		FEV_1		MMF		RV	
					B	R	B	R	B	R	B	R
	°C	*mg/liter*	*liters/min*	*beats/min*	*liters/s per cm H_2O/liter*		*liters*		*liters/s*		*liters*	
1	23.5	6.7	62.2	160	0.14	0.04	2.22	1.84	1.09	0.92	2.06	2.77
2	25.0	5.3	55.4	146	0.16	0.08	2.65	2.42	1.87	1.49	1.08	1.26
3	25.0	5.3	71.2	174	0.12	0.04	2.55	2.07	1.89	1.09	1.32	1.71
4	23.0	8.8	75.4	158	0.11	0.06	3.13	2.02	2.45	1.15	1.91	3.82
5	23.0	9.0	75.7	164	0.13	0.07	2.69	2.31	1.78	1.35	1.74	2.46
6	24.0	9.3	78.7	176	0.14	0.05	2.72	1.39	2.41	0.66	1.01	2.98
7	23.0	7.6	82.8	162	0.13	0.06	2.98	2.01	2.27	1.22	1.76	2.23
8	23.0	8.6	69.2	180	0.09	0.04	1.74	1.50	0.91	0.87	1.12	2.19
Mean	23.7	7.6	71.3	165	0.13	0.06	2.59	1.95	1.83	1.09	1.50	2.43
SD	0.9	1.6	9.0	11	0.02	0.02	0.44	0.36	0.58	0.27	0.41	0.79
P	—	—	—	—	<0.001		<0.005		<0.01		<0.01	

The *P* values refer to base line-response comparisons. B, base line; R, response.

temperature fully saturated and body temperature fully saturated) for this index.

The trend in our data can be more clearly seen when the changes in each variable are pooled and plotted as a percent of the control experimental response versus the inspired water content. As can be seen in Fig. 4, when the water content doubled, the observed bronchospastic response approximately halved. When it was again doubled to its maximum limit, obstruction did not develop.

It is unlikely that the differences in the magnitude of the response recorded above were due to variations in the application of the exercise stimulus. One factor analysis of variance demonstrates that there were no significant differences in either $\dot{V}E$ or heart rates between any study ($\dot{V}E$, $F = 0.54$; $df = 3,31$; P NS; HR, $F = 0.30$; $df = 3,31$; P NS).

Further, it is also unlikely that our results were due to an improvement in pre-exercise lung function brought about by inhaling the test gases. Fig. 5 demonstrates that peak flows did not change in any of the experiments during the 4 min that the subjects were breathing on the exchanger at rest ($F < 1.0$ for all comparisons by two factor analysis).

TABLE II

Effects of Exercise on Pulmonary Mechanics While Breathing Air at Body Temperature and Ambient Water Content

Subject	T	WC	$\dot{V}_E$	HR	SG_{aw}		FEV_1		MMF		RV	
					B	R	B	R	B	R	B	R
	°C	*mg/liter*	*liters/min*	*beats/min*	*liters/s per cm H_2O/liter*		*liters*		*liters/s*		*liters*	
1	37.0	6.9	65.3	152	0.15	0.04	2.40	1.12	1.37	0.46	1.60	3.21
2	37.5	9.2	67.2	142	0.14	0.06	2.29	1.73	1.37	0.89	1.09	1.74
3	37.5	9.2	76.1	168	0.11	0.04	2.68	1.60	2.06	0.73	1.49	2.47
4	37.0	8.6	93.4	168	0.11	0.07	3.73	2.96	3.00	2.18	1.69	2.83
5	37.5	9.2	67.5	164	0.12	0.09	2.51	2.30	1.63	1.45	1.66	2.00
6	37.5	8.8	70.6	166	0.13	0.04	2.82	1.56	2.46	0.94	1.53	3.15
7	37.5	9.0	81.7	162	0.12	0.06	2.75	2.68	2.05	1.75	1.77	2.04
8	37.5	8.8	60.4	174	0.08	0.04	1.75	1.51	0.88	0.79	1.18	1.98
Mean	37.4	8.7	72.7	162	0.12	0.06	2.62	1.93	1.85	1.15	1.50	2.43
SD	0.2	0.8	10.6	10	0.02	0.02	0.56	0.64	0.68	0.59	0.24	0.57
P	—	—	—	—	<0.001		<0.01		<0.01		<0.005	

The *P* values refer to base line-response comparisons. B, base line; R, response.

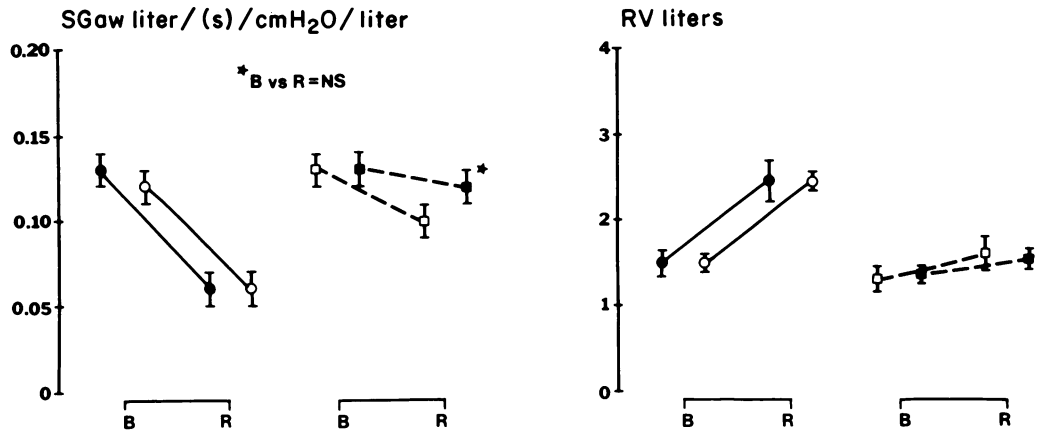

FIGURE 2 Changes in specific conductance (SG_{aw}) and residual volume (RV) after exercise while inspiring air of various temperatures and water contents. The letters B and R below each graph represent base-line and response values, respectively. The data points are mean values, and the brackets represent 1 SE. (●) Ambient temperature and water content; (○) body temperature ambient water content; (□) ambient temperature saturated; (■) body temperature saturated.

DISCUSSION

The results of this study demonstrate that the magnitude of the bronchospastic response of asthmatics to exercise can be considerably blunted by increasing the water content of inspired air at ambient room temperatures and totally abolished by having the subjects inhale air at BTPS conditions. Although we have insufficient data to state categorically that these observations are causally related to the phenomenon of exercise-induced asthma, consideration of the factors that determine the physiology of heat and water exchange in the airways, in conjunction with the chronic mucosal changes seen in this illness (11, 12), suggest that our findings may explain part of the reaction sequence by which physical exertion ultimately leads to airway obstruction.

During inspiration, air is conditioned to have a temperature of 37°C and 44 mg of water/liter by the time it reaches the alveoli. This is accomplished by transferring sufficient quantities of heat and water from the respiratory mucosa to correct for the differences in temperature and humidity between the ambient air and that of the body per unit volume inhaled. Heating appears to occur primarily by convection which is greatly facilitated by the turbulent flows and large temperature gradients that are found in the upper air passages (13, 14). As the air is warmed, its capacity to hold water increases, and it is humidified by evaporation from the airway lining. The net effect of this heat

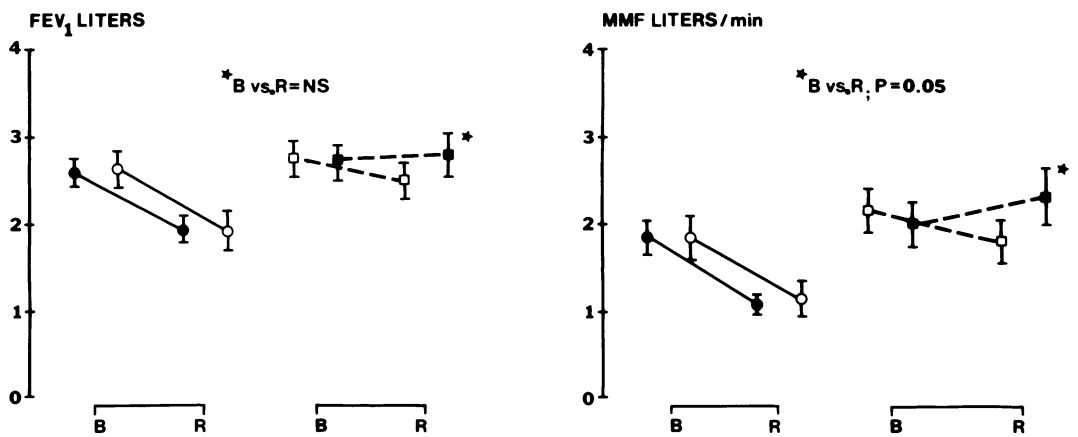

FIGURE 3 Changes in 1-s forced expiratory volumes (FEV_1) and maximum mid-expiratory flow rates (MMF) after exercise while inspiring air at various temperatures and water contents. The format is identical to Fig. 2.

TABLE III

Effects of Exercise on Pulmonary Mechanics While Breathing Air at Ambient Temperature Fully Saturated

Subject	T	WC	$\dot{V}_E$	HR	SG_{aw}		FEV_1		MMF		RV	
					B	R	B	R	B	R	B	R
	°C	mg/liter	liters/min	beats/min	liters/s per cm H_2O/liter		liters		liters/s		liters	
1	23.0	20.5	56.3	168	0.14	0.08	2.36	2.03	1.28	0.95	—	—
2	23.0	20.5	71.0	144	0.11	0.11	2.16	2.00	1.23	1.16	1.06	1.23
3	22.0	19.5	76.4	168	0.12	0.08	2.73	2.63	2.47	2.11	1.49	1.82
4	23.0	20.5	83.9	164	0.10	0.09	3.90	3.46	3.34	2.45	1.31	1.99
5	23.0	20.5	76.4	156	0.17	0.15	2.77	2.50	2.18	1.50	1.38	1.45
6	23.0	20.5	71.8	148	0.16	0.11	3.16	2.93	2.94	2.99	1.06	1.37
7	23.0	20.5	71.5	164	0.10	0.06	2.67	2.44	2.00	1.57	1.92	2.34
8	23.0	20.5	60.3	172	0.14	0.10	2.30	2.17	1.80	1.49	0.92	1.02
Mean	22.9	20.4	71.0	161	0.13	0.10	2.76	2.52	2.16	1.78	1.31	1.60
SD	0.4	0.4	8.9	10	0.03	0.03	0.56	0.50	0.75	0.69	0.34	0.46
P	—	—	—	—	<0.005		<0.001		<0.01		<0.01	

The *P* values refer to base line-response comparisons. B, base line; R, response.

and water exchange is to cool the mucosa. During expiration the process reverses along thermal gradients by convection, and as the air temperature falls, its water capacity so diminishes that condensation onto the mucosa ensues. This results in recovery by the mucosa of between one-third and one-half of the heat transferred to the air during inspiration (15). Of the two processes required to condition the inspirate, i.e., direct heating of the inspired air (0.304 cal/liter per °C) and the latent heat of vaporization of water 0.58 Kcal/g, the latter predominates; thus, the vast majority of the heat transferred by the mucosa is in the form of latent heat of vaporization. Hence, it should be no surprise that in pre-conditioning the air, the effects of humidity on the bronchospastic response predominated over temperature alone.

Matching inspired temperature to that of the body would be expected to decrease the heat transfer across the mucosa only very little. By contrast, increasing the water content of the inspirate, even at ambient temperatures, greatly decreases the heat transfer. Hence, the findings that humidity and not temperature influenced lung function are consistent with the idea that the quantity of heat transferred across the mucosal surface is a major determinant of the magnitude of the bronchospastic response after exercise.

Why does bronchoconstriction develop under these circumstances in asthmatics and not in normal subjects?

TABLE IV

Effects of Exercise on Pulmonary Mechanics While Breathing Air at Body Temperature Fully Saturated

Subject	T	WC	$\dot{V}_E$	HR	SG_{aw}		FEV_1		MMF		RV	
					B	R	B	R	B	R	B	R
	°C	mg/liter	liters/min	beats/min	liters/s per cm H_2O/liter		liters		liters/s		liters	
1	37.0	44	55.4	142	0.13	0.14	2.12	2.21	0.97	1.09	1.61	1.81
2	38.0	46	57.1	152	0.14	0.12	2.63	2.78	1.62	2.04	1.10	1.21
3	37.0	44	82.9	180	0.17	0.10	2.86	3.04	2.35	2.88	1.18	1.37
4	37.0	44	64.1	172	0.10	0.11	3.67	4.20	3.06	3.65	1.51	1.83
5	37.5	45	69.8	156	0.11	0.14	2.62	2.64	1.94	2.00	1.27	1.56
6	36.5	43	58.0	170	0.21	0.14	2.89	2.90	2.92	3.40	—	—
7	37.0	44	78.4	164	0.11	0.12	3.00	2.89	1.79	2.41	1.61	1.74
8	36.5	43	69.2	184	0.09	0.09	1.92	1.81	1.13	1.01	1.05	1.19
Mean	37.1	44.1	66.9	165	0.13	0.12	2.71	2.81	1.97	2.31	1.33	1.53
SD	0.5	1.0	10.1	14	0.04	0.02	0.54	0.70	0.76	0.98	0.24	0.28
P	—	—	—	—	NS		NS		<0.02		<0.001	

The *P* values refer to base line-response comparisons. B, base line; R, response.

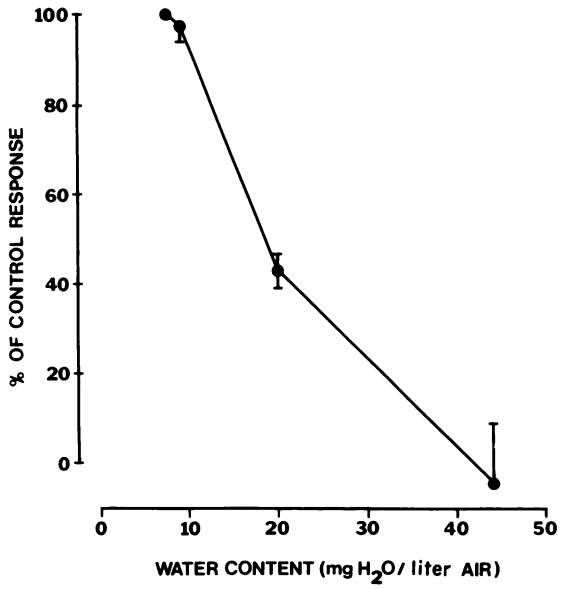

FIGURE 4 Comparison of the percentage change in response from the control observation as a function of increasing inspired water content. The data points represent the mean change seen when all indices of pulmonary mechanics were pooled. The brackets represent 1 SEM.

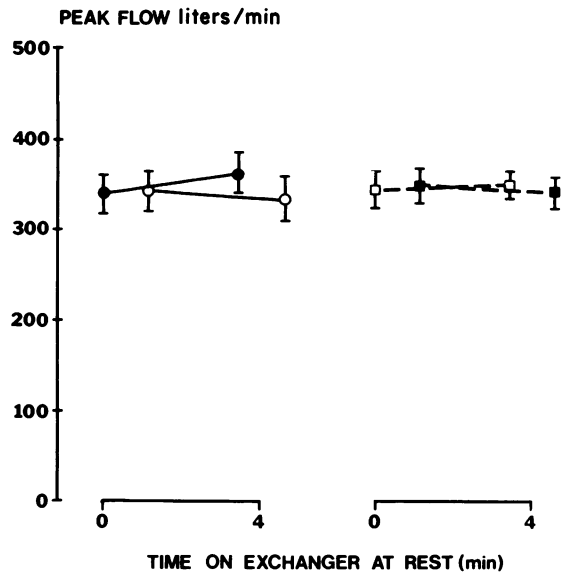

FIGURE 5 Comparison of the effects of breathing air at various temperatures and water contents on resting lung function. The data points are mean values and the brackets represent 1 SE. Zero time represents data obtained immediately after the subjects went on the exchanger and the 4-min values are those that were obtained immediately before exercise. (●) Ambient temperature and water content; (○) body temperature ambient water content; (□) ambient temperature saturated; (■) body temperature saturated.

Theoretically, there are three possibilities. Because of the pathologic changes in their airways, asthmatics may not: (*a*) condition the inspired air normally; (*b*) recover as much heat and (or) water on expiration as do normals; or (*c*) they may be unusually sensitive to effects of the physical stimulus of cooling. There are no data in the literature to prove any of these points, but it is of interest that Caldwell et al. found the fraction of body heat dissipated by way of the respiratory tract to be higher in patients with lung disease than it is in normals (16). On the average, the ventilations in the present study were six times greater than in Caldwell's work, and it is to be expected that the heat loss was also commensurately greater.

At this time there is insufficient information available in the literature to determine if the defect in conditioning inspired air results only from mucosal inflammatory changes which might cause a fault in regulation, or from insufficient quantities of heat being supplied to the surface of the airways by a defective blood supply. Given the fact that submucosal capillaries are known to be dilated in this condition (11, 12), the latter seems unlikely. However, until precise data on mucosal blood flow in relation to tissue mass is forthcoming, this factor remains a consideration.

Within the framework of the hypothesis that conditioning of inspired air may be defective in asthmatics, it seems pertinent to consider the differences in the response to ambient air exercise in two groups of subjects previously reported from this laboratory, because representatives of both are included in the present study (9). One group developed after exercise predominantly large airway obstruction that was totally abolished by a parasympatholytic and the other had a predominantly small airway response which was not affected by pretreatment with anticholinergics. It is tempting to speculate that in the first group, heat transfer and its effects were predominant in large airways where the density of irritant receptors is greatest (17). By contrast, it is possible that incompletely conditioned air penetrated more deeply into the respiratory tract of the small airway group, and direct or local effects accounted in large part for the response.

It is not at all certain that these two groups are immutable. It is feasible that the severity of the illness before challenge dictated the location of the responses. For example, the patients with predominant small airway obstruction had more impaired lung function before challenge than did the large airway group. Consequently, in the former, it is reasonable to suggest that inflammatory process with the airways accounted for an insufficient conditioning of air until it reached more distal portions of the tracheobronchial tree. If this were true, then the site of obstruction induced by exercise would be expected to change as the patient's underlying disease process waxes and wanes.[2]

[2] McFadden, E. R., Jr., and R. H. Ingram, Jr. Unpublished observations.

Inasmuch as both populations had their responses blunted by cromolyn sodium, it appears likely that irrespective of site, mediator release is involved in bringing about the bronchospasm, or that other less specific effect of cromolyn was involved. The concept of mast cells being activated by nonimmunologic stimuli in these circumstances is an intriguing one. It has been recently shown that there are histamine-containing cells that are related to the mast cell-basophil series that can be readily lavaged from bronchial lumens of humans (18), and it is possible that they could be directly stimulated by the thermal conditions of their environment. Precedent for this reasoning can be derived from conditions like cold-induced urticaria and cholinergic urticaria in which the chemical mediators of immediate hypersensitivity are released from mast cells within the skin in response to cold and heat, respectively (19, 20).

Irrespective of the ultimate path by which the obstruction develops, even if our findings are not causally related to the phenomenon of exercise-induced asthma, they clearly demonstrate that environmental conditions extraneous to the patient can profoundly influence the magnitude of the response. These conclusions are similar to those reached in a recent abstract (21). The clinical significance of these observations is that when one is attempting to determine such basic issues as reproducibility, prevalence, and effects of various therapeutic maneuvers by performing exercise challenges spaced over days, variations or fluctuations in environmental temperature and humidity are significant interactive variables that must be controlled. As our knowledge expands, it is expected that these climatic factors will be found to be unique to exercise because of the stress it puts upon the heat exchanging mechanisms of the respiratory tract and will play little or no role in other forms of bronchial challenges.

ACKNOWLEDGMENTS

This study was supported in part by grants HL 17873, 17382, and 07010 from the National Heart, Lung, and Blood Institute of the National Institutes of Health.

REFERENCES

1. Strauss, R. H., E. R. McFadden, Jr., R. H. Ingram, Jr., and J. J. Jaeger. 1977. Enhancement of exercise-induced asthma by cold air breathing. *N. Engl. J. Med.* **297:** 743–747.
2. American Thoracic Society. 1962. Definitions and classifications of chronic bronchitis, asthma, and pulmonary emphysema. *Am. Rev. Respir. Dis.* **85:** 762–768.
3. DuBois, A. B., S. Y. Botelho, G. N. Bedell, R. Marshall, and J. H. Comroe, Jr. 1956. A rapid plethysmographic method for measuring thoracic gas volume: A comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. *J. Clin. Invest.* **35:** 322–326.
4. Sykes, W. T., R. L. Haynes, and E. R. McFadden, Jr. 1977. On line determination of lung volumes by plethysmography and digital computer. *Am. Rev. Respir. Dis.* **115:** 581–585.
5. Briscoe, W. A., and A. B. DuBois. 1958. The relationship between airway resistance, airway conductance, and lung volume in subjects of different age and body size. *J. Clin. Invest.* **37:** 1279–1285.
6. Strauss, R. H., R. L. Haynes, R. H. Ingram, Jr., and E. R. McFadden, Jr. 1977. Comparison of arm versus leg work in induction of acute episodes of asthma. *J. Appl. Physiol.* **42:** 565–570.
7. Strauss, R. H., R. H. Ingram, Jr., and E. R. McFadden, Jr. 1977. A critical assessment of the roles of circulating hydrogen ion and lactate in the production of exercise-induced asthma. *J. Clin. Invest.* **60:** 658–664.
8. Haynes, R. L., R. H. Ingram, Jr., and E. R. McFadden, Jr. 1976. An assessment of the pulmonary response to exercise in asthma and an analysis of the factors influencing it. *Am. Rev. Respir. Dis.* **114:** 739–752.
9. McFadden, E. R., Jr., R. H. Ingram, Jr., R. L. Haynes, and J. J. Wellman. 1977. Predominant site of flow limitation and mechanisms of postexertional asthma. *J. Appl. Physiol.* **42:** 746–752.
10. Kagawa, J., and H. D. Kerr. 1970. Effect of brief-graded exercise on specific airway conductance in normal subjects. *J. Appl. Physiol.* **28:** 138–144.
11. Dunnill, M. S. 1975. The morphology of the airways in bronchial asthma. *In* New Directions in Asthma. M. Stein, editor. American College of Chest Physicians, Park Ridge, Ill. 213–221.
12. Dunnill, M. S. 1960. The pathology of asthma, with special reference to changes in the bronchial mucosa. *J. Clin. Path. (Lond.).* **13:** 27–33.
13. Proetz, A. W. 1951. Air currents in the upper respiratory tract and their clinical importance. *Ann. Otol. Rhinol. Laryngol.* **60:** 439–467.
14. Gaensler, E. A., J. V. Maloney, Jr., and V. O. Bjork. 1952. Bronchospirometry. Experimental observations and theoretical considerations of resistance to breathing. *J. Lab. Clin. Med.* **39:** 935–953.
15. Cole, P. 1953. Further observations on the conditioning of respiratory air. *J. Laryngol. Otol.* **67:** 669–681.
16. Caldwell, P. R. B., D. M. Gomez, and H. W. Fritts, Jr. 1969. Respiratory heat exchange in normal subjects and in patients with pulmonary disease. *J. Appl. Physiol.* **26:** 82–88.
17. Mortola, J., G. Sant'Ambrogio, and M. G. Clement. 1975. Localization of irritant receptors in the airways of the dog. *Resp. Physiol.* **24:** 107–114.
18. Patterson, R., J. M. McKenna, I. M. Suszko, N. H. Solliday, J. J. Pruzansky, M. Roberts, and T. J. Kehoe. 1977. Living histamine containing cells from the bronchial lumens of humans. *J. Clin. Invest.* **59:** 217–225.
19. Soter, N. A., and K. F. Austen. 1977. Urticaria, angioedema, and mediator release in humans in response to physical environmental stimuli. *Fed. Proc.* **36:** 1736–1740.
20. Wasserman, S. I., N. A. Soter, D. M. Center, and K. F. Austen. 1977. Cold urticaria. Recognition and characterization of a neutrophil chemolactic factor which appears in the serum during experimental cold challenge. *J. Clin. Invest.* **60:** 189–196.
21. Chen, W. Y., D. J. Horton, and J. F. Souhrada. 1976. Respiratory heat and water loss and exercise-induced asthma. *Physiologist.* **19:** 152. (Abstr.)