Thermally Induced Asthma and Airway Drying

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The purpose of this study was to determine whether mucosal dehydration causes thermally induced asthma. To provide data on this point, we studied the effects on lung function of progressive water loss (W_L) from the respiratory tract by having eight subjects perform isocapnic hyperventilation for 1, 2, 4, and 8 min at a constant level ($\dot{V}_E$ = 57.5 ± 6.3 L/min [mean ± SEM]) while they breathed dry air at frigid (T_I = −12.5 ± 2.7° C) (cold trial) and ambient (24.3 ± 0.7° C) (warm trial) temperatures. Expired temperatures (T_E) were continuously monitored, and W_L from the intrathoracic airways was calculated from published relationships. FEV_1 was measured before and after each challenge. Each inspirate produced stimulus–response decrements in FEV_1, but the effect of cold air was greater (% Δ $cold_{8min}$ = 30.0 ± 4.7%, warm = 16.0 ± 4.4%; p = 0.01). Water loss, however, was significantly less in the cold experiment because T_E was lower (W_L $cold_{8min}$ = 4.8 ± 0.4 g, warm = 7.1 ± 0.7 g; p = 0.001; T_E $cold_{8min}$ = 22.8 ± 2.3° C, warm 30.9 ± 1.5° C; p = 0.003). The FEV_1 decreased as W_L rose, but the largest intrathoracic losses were associated with the smallest obstructive response (% ΔFEV_1 $cold_{8min}$ = 30%, W_L = 4.7 mg; % ΔFEV_1 $warm_{8min}$ = 16%, W_L = 7.1 mg; p = 0.002). These data show that removal of water from the lower respiratory tract, and by inference the development of a hyperosmolar periciliary fluid, do not appear to be the primary causes of thermally induced asthma. McFadden ER, Jr., Nelson JA, Skowronski ME, Lenner KA. Thermally induced asthma and airway drying. AM J RESPIR CRIT CARE MED 1999;160:221–226.

Strenuous physical exertion is one of the most common triggers of acute episodes of asthma (1). Yet despite the great increase in understanding that has occurred in recent years about the factors at work in producing and sustaining this disease, the means by which thermal triggers (i.e., exercise and hyperventilation) elicit airway narrowing continue to elude description. All investigators agree that the heat flux, and the concomitant mucosal cooling, associated with increased minute ventilation ($\dot{V}_E$) are critical initial components of the process that leads to narrowing (2–8), but the manner in which these phenomena are translated into symptomatic obstruction remains obscure. One popular theory holds that the mechanism of airway narrowing derives from hyperpnea-induced evaporation of the periciliary fluid, with a resultant increase in surface osmolarity and mast cell degranulation (2, 3, 9, 10). The strengths and weaknesses of this hypothesis have been debated without resolution of its validity (1, 3, 9–12), and it is unlikely that further analyses of the available data will lead to consensus.

In the present study, we sought to shed new light on this topic by isolating the process of evaporation and examining the manner in which asthmatic subjects react to controlled water losses at different thermal burdens. This was accomplished by having a group of subjects inhale dry air at different temperatures. With this procedure, the total amount of water vaporized in each instance would be identical, at 44 mg/L, but the heating requirements of the inspirates would be different. We postulated that if mucosal dehydration were critical to airway narrowing in asthma, then incremental hyperventilation of dry frigid and dry warm air should result in identical and progressive increases in epithelial-fluid tonicity that would induce proportional and equal decrements in pulmonary mechanics in both circumstances. In this paradigm, gas temperature would not have a major impact. Alternatively, if desiccation were not an issue, and other factors such as increased capillary permeability were important (7, 11, 13), then the intensity of the airflow limitation would vary between experiments solely as a function of the temperature of the inspired air (2, 12, 14). Our observations form the basis of this report.

METHODS

Eight atopic asthmatic subjects (five females and three males), aged 28 ± 2 yr (mean ± SEM), served as our subjects in a three-part investigation. Each participant gave a history of exercise-induced asthma and had normal predicted values (92 ± 4%) of FEV_1 at the time of investigation. None had experienced an upper respiratory tract infection in the 6 wk preceding the study, and all refrained from medications for 12 h before each study day. During the screening phase, stimulus–response curves for isocapnic hyperventilation were generated while the subjects inhaled cold air through a heat exchanger (6, 11, 13). As in former studies, each bout of hyperpnea lasted 4 min, and the expired air was directed into a reservoir balloon that was constantly evacuated at a known rate through a calibrated rotameter (6, 8, 11–13). The participants were coached to keep the balloon filled, and in

(*Received in original form October 14, 1998 and in revised form February 2, 1999*)

Supported in part by grants HL-33791 and HL-44920 from the National Heart, Lung and Blood Institute, and General Clinical Research Center Grant M01 RR00080 from the National Center for Research Resources, United States Public Health Service.

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so doing, their $\dot{V}_E$ could be controlled at any desired level (8, 11, 13). End-tidal CO_2 concentrations ($P_{ET_{CO_2}}$) during hyperventilation were monitored with an LB-2 analyzer (Beckman Instruments, Inc., Fullerton, CA), and sufficient CO_2 was added to the inspiratory port of the exchanger to maintain eucapnic levels ($P_{ET_{CO_2}}$ = 40 to 42 mm Hg).

Maximum forced exhalations were performed in triplicate, with a waterless spirometer used before and serially after each period of hyperventilation. The curve with the largest FEV_1 was chosen for analyses.

When the foregoing data had been obtained, the subjects returned to the laboratory on two additional occasions and generated temporal stimulus–response curves for isocapnic hyperventilation at the maximum $\dot{V}_E$ achieved in the screening phase of the study. In this instance, they hyperventilated for 1, 2, 4, and 8 min, in that order. On one day, subjects inhaled frigid gas (cold trial), and on the other, dry air at room temperature was administered (warm trial). The order of study was randomly determined. Each trial of hyperpnea was separated from the next by 40 to 60 min. Spirometry was done before and 10, 15, 30, 45, and 60 min after each period of hyperventilation until the FEV_1 returned to baseline (i.e., ≤ 5% of its prechallenge value). At this point the next challenge began. The data recorded 10 min after challenge were used for analysis, to provide a uniform point of reference. Statistically, this point tends to coincide with the maximum obstructive response (8).

Dry, warm air was generated by bleeding compressed air from a gas cylinder into a large reservoir balloon and feeding the air into the inspiratory port of the heat exchanger, which had been set to match the usual temperature of the laboratory (i.e., 24 to 26° C) (6–8, 13). The water content of the inspirate during hyperpnea in both the cold and warm air experiments was less than 1 mg H_2O/L, which for the purpose of this study was considered to be zero. Recovery from each challenge took place in ambient conditions (temperature 24 to 26° C, relative humidity 40 to 60%).

The temperatures of the inspired (T_I) and expired (T_E) air were continuously measured with a rapidly responding copper–constantin thermocouple made of 0.005-in. wire (Omega Engineering, Inc., Stamford, CT), situated in the mouthpiece of the heat exchanger, and were displayed on a strip-chart recorder (Omega Model 585; Omega Engineering) (6–8, 13). The data during each minute of hyperventilation were recorded and then averaged to determine a mean value for the 1-, 2-, 4-, and 8-min trials, respectively. The water losses associated with each period of hyperpnea were computed from standard temperature–water vapor relationships, using Equation 1 and assuming the expired air to be fully saturated at its existing temperature (3, 6–8, 15). Since the distribution of water movement within the tracheobronchial tree in normal and asthmatic subjects has been mapped (7, 8), the calculations were modified to reflect the source of the losses.

$$W_L = ([Wci - Wce] \cdot \dot{V}_E \cdot Time) \cdot 0.5 \quad (1)$$

Where: W_L = the volume of water lost to the environment in mg/L air; Wci = the inspired water content in mg/L air; Wce = the expired water content in mg/L air; $\dot{V}_E$ = minute ventilation in L/min; Time = the duration of hyperventilation in minutes; and 0.5 = the percentage of water lost from the intrathoracic airways (7, 8).

The study was approved by the Institutional Committee for Human Research, University Hospitals of Cleveland, and informed consent was obtained from each subject.

The study data were analyzed with one-factor analyses of variance (ANOVA), linear regression, repeated measures trend analysis, and paired *t* tests. All p values were two sided, and a value of $p \leq 0.05$ was considered significant.

RESULTS

Table 1 presents the $\dot{V}_E$ values and prechallenge lung function results for the cold and warm air experiments. The subjects' resting $\dot{V}_E$ was 8.7 ± 2.3 L/min before the cold trial and 11.1 ± 1.4 L/min before the warm trial, and varied from 40 to 80 L/min during hyperpnea (mean: 57.7 ± 6.3 L/min). Each subject's $\dot{V}_E$ was held constant both within and between studies. The FEV_1 before the cold and warm provocations was statistically identical, and ranged between 92 ± 4% and 88 ± 4% predicted.

The temporal stimulus–response curves for the cold and warm air experiments are shown in Figure 1 in absolute and relative terms. As can be seen, both inspired air conditions altered lung function, and as the time spent in hyperventilating increased, the severity of bronchial narrowing increased. In the cold trial (T_I = −12.5 ± 2.7° C), each data point was significantly different from the control (F = 5.8, p = 0.001; factorial analysis), and the FEV_1 fell from 3.18 ± 0.14 L to 2.24 ± 0.21 L. This was not the case in the warm experiment (T_I = 24.3 ± 0.7° C) (F = 1.42; p = 0.25). Here, the decreases in FEV_1 after 2, 4, and 8 min of hyperventilation were statistically significant by paired comparisons ($p \leq 0.005$ for each), but the 1-min value was not. When the data for the warm trial were transformed into percentage changes, the overall dose–response effect became significant (F = 3.80; p = 0.02). The FEV_1 values before the 8-min experiments in the cold and warm trials were within 3% (3.09 ± 0.11 L) and 2% (3.01 ± 0.13 L) of their original baselines, respectively.

TABLE 1

CLINICAL AND PRECHALLENGE DATA

			Cold Trial		Warm Trial	
Patient	Age	Hx of EIA	$\dot{V}_E$	FEV_1	$\dot{V}_E$	FEV_1
1	24	+	80	3.46	80	3.86
2	29	+	40	3.42	40	3.39
3	26	+	60	2.88	60	2.86
4	22	+	40	2.95	40	2.79
5	32	+	60	2.64	60	2.69
6	42	+	40	2.88	40	2.76
7	27	+	80	3.59	80	3.49
8	24	+	60	3.62	60	2.72
Mean	28	—	57.5	3.18	57.5	3.07
SEM	2		6.3	0.14	6.3	0.17

Definition of abbreviations: FEV_1 = baseline value for FEV_1 prior to the cold and warm air trials; Hx of EIA = history of exercise-induced asthma; $\dot{V}_E$ = minute ventilations used during each period of hyperpnea.

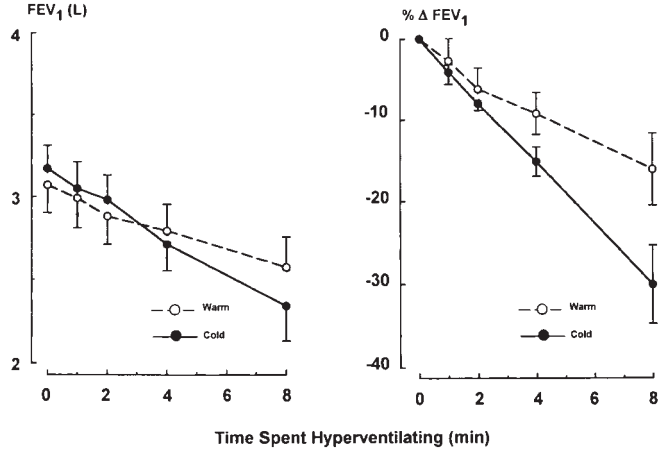

Figure 1. The effect of varying the time of hyperventilation with dry air on lung function. The ordinates depict FEV_1 in liters, as well as the percent change from baseline. The abscissa is the time spent hyperventilating in minutes. The zero time point represents the prechallenge baseline. The data points are mean values and the brackets represent 1 SEM. The mean values for the inspired temperatures and minute ventilations are $\dot{V}_E$ = 57.5 ± 6.3 L/min; cold T_I = −12.5 ± 2.7° C, WC_i = 0; warm T_I = +24.3 ± 0.7° C, WC_i = 0.

Comparison of the cold and warm trial results showed that the slopes of the cold and warm relationships between duration of hyperventilation and FEV_1 were significantly different from each other for both representations upon repeated measures trend analysis (cold versus warm absolute data: $F = 10.1$, $p = 0.01$; $\%\Delta$ data: $F = 10.7$, $p = 0.01$). There were no differences between studies for the 1- and 2-min points, but by 4 min of hyperpnea, the curves began to dissociate (4 min cold: $\%\Delta\ FEV_1 = 15.1 \pm 1.8\%$; warm: $\%\Delta\ FEV_1 = 9.2 \pm 2.6\%$; $p = 0.07$, paired comparison), and by 8 min, hyperventilation with cold dry air produced significantly greater airflow limitation than did inhaling warm dry air for the same time $\times$ $\dot{V}_E$ product (8 min cold: $\%\Delta\ FEV_1 = 30.0 \pm 4.7\%$; warm: $\%\Delta\ FEV_1 = 16.0 \pm 4.4\%$; $p = 0.01$, paired comparison).

The temperatures of the inspired and expired air for each period of hyperpnea are shown in Figure 2. Since T_I was being controlled by the heat exchanger, the differences between inspirates were continuously maintained, and there was little within-experiment variation (T_I resting: cold $= -11.5 \pm 1.8°$ C, 8 min $= -11.6 \pm 2.6°$ C; T_I resting: warm $= 24.9 \pm 0.69°$ C, 8 min $= 24.4 \pm 0.69°$ C). This was not the case during expiration. As the subjects began to hyperventilate, T_E fell and then decreased further as the time spent hyperventilating lengthened. These changes were most marked in the cold trial. In this experiment, T_E was significantly lower than in the warm trial at all levels of hyperpnea (cold T_E: min 1 $= 28.3 \pm 2.3°$ C; warm T_E: min 1 $= 32.3 \pm 0.9$; $p = 0.04$; cold T_E: min 8 $= 22.8 \pm 2.3$; warm T_E: min 8 $= 30.9 \pm 1.5$; $p = 0.002$, paired comparisons). Further, the total decline in T_E was more extreme with cold air (i.e., ΔT_E cold from 1 min to 8 min $= 5.3°$ C; ΔT_E warm $= 1.3°$ C; $p = 0.001$, paired comparisons).

Figure 3 presents the data on intrathoracic water movement. When $\dot{V}_E$ increased, W_L followed suit. At rest and during 1 min of hyperpnea, the water losses in the cold and warm experimental arms were small and within 0.11 g of each other. As the duration of ventilation increased, intrathoracic losses increased significantly in a stimulus–response manner in both trials (cold trial: $F = 73$; $p < 0.001$; warm trial: $F = 49$; $p < 0.001$, factorial analysis). The quantity of water exhaled, however, was consistently greater with the room air inspirate ($F = 16.23$, $p = 0.005$, repeated measures trend analysis). At the end of 8 min of hyperpnea with cold dry air, 4.8 ± 0.4 g of H_2O was removed from the intrathoracic airways and lost. With warm dry air, this value was 7.1 ± 0.7 g. On a point-by-point basis, W_L was 15%, 48%, 55%, and 49% greater with the warm inspirate after 1, 2, 4, and 8 min of hyperventilation, respectively, than it was with the cold inspirate.

The relationship of water loss to airway obstruction is presented in Figure 4. As expected, as losses increased, FEV_1 progressively fell (group data: $r = 0.30$, $F = 7.36$, $p = 0.008$), but the patterns seen with the warm and cold inspirates differed markedly. The cold air curve was shifted significantly downward and to the left ($F = 17.31$, $p = 0.004$, repeated measures trend analysis). At 2 min of hyperpnea (Figure 4, third set of data points), W_L was significantly different in the two trials (cold: 1.48 ± 0.12; warm: 2.09 ± 0.25 g; $p = 0.01$) for virtually the same change in FEV_1 (cold: $8.0 \pm 0.8\%$, warm: $6.2 \pm 2.6\%$, $p = 0.55$). After 4 min of hyperventilation (Figure 4, fourth set of data points), the discrepancies between inspirates for both W_L and FEV_1 widened further, and after 8 min of cold dry air, 4.8 ± 0.4 g of H_2O was exhaled, with a 30% decrement in FEV_1. In contrast, inhaling warm dry air for the same product of $\dot{V}_E \times$ time caused a 49% greater water loss (7.1 ± 0.7 g) but evoked almost 50% less obstruction ($\Delta FEV_1 = 16.0 \pm 4.4\%$) ($p = 0.003$).

DISCUSSION

The results of the present study show that the removal of water from the lower respiratory tract, and, by inference, the development of a hyperosmolar periciliary fluid, do not appear to be the primary causes of thermally induced asthma. Clearly,

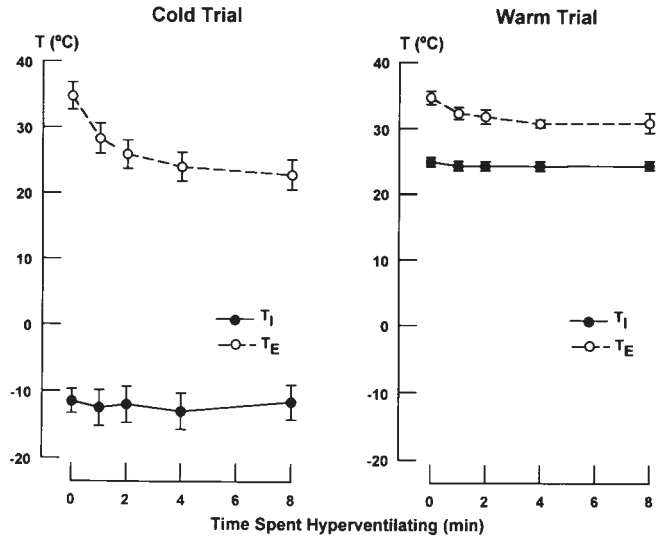

Figure 2. Temperatures of inspired and expired air during hyperpnea in the cold and room air trials. The ordinates show temperature in degrees centigrade and the abscissa is the time spent hyperventilating in minutes. Zero time indicates the values obtained at resting ventilations before hyperpnea. The *solid circles* and *solid lines* represent the temperature of the inspired air (T_I), whereas the *open circles* and *broken lines* display expired temperature (T_E). The data points are mean values, and the brackets represent 1 SEM.

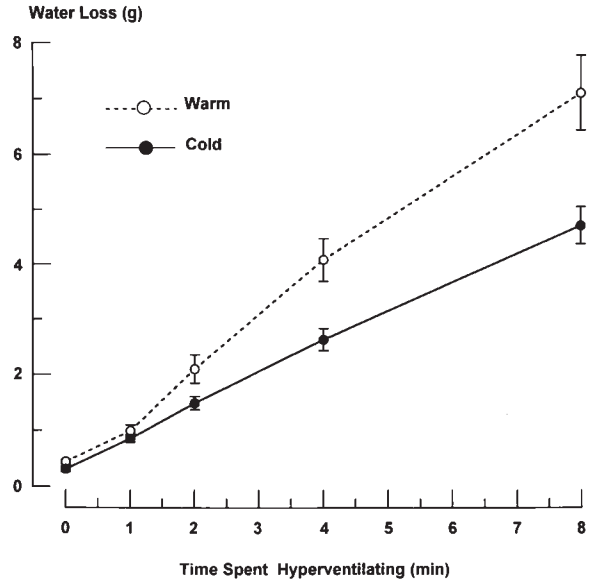

Figure 3. Water losses from the intrathoracic airways. The ordinate is water loss in grams and the abscissa is the time spent hyperventilating in minutes. Zero time indicates the values obtained at resting ventilations before hyperpnea. The data points are mean values and the brackets represent 1 SEM. The *solid circles* and *solid lines* represent the cold dry air experiment and the *open circles* and *broken lines* represent the warm dry air trial.

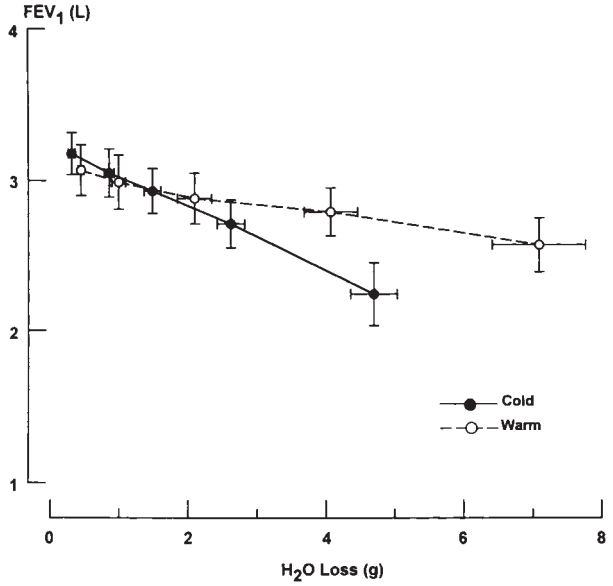

Figure 4. The influence of intrathoracic water losses on lung function. The ordinate is FEV_1 in liters, and the abscissa is water loss in grams. Zero time indicates the values obtained at resting ventilations before hyperpnea. The data points are mean values and the brackets represent 1 SEM. The cold experiment is shown by the *closed circles* and *solid lines* and the warm trial is represented by the *open circles* and *broken lines*.

water fluxes are an important feature of the reaction sequence leading to bronchial narrowing in this condition (6–8) (Figure 4), but only to the extent that evaporation contributes to airway cooling and rewarming (6–8, 12). The issue of dehydration *per se* does not appear to be of major consequence.

We appreciate that our study did not address the issue of whether airway drying occurs with hyperpnea, and that it will take direct measures of airway surface fluid movement and ionic content to answer this question. Nonetheless, our data do show that whether they occur or not, such events do not seem to play much of a role in the pathogenesis of exercise-induced asthma. Our protocol was designed to test as fully as possible the assumptions underlying the hyperosmolar theory. Dry inspirates and progressive minute ventilations were used because the former require that the maximum amount of water be vaporized to completely saturate the incoming air, and the latter exhaustively stress the ability of the tracheobronchial tree to replace intrathoracic losses (3, 4, 6–10, 12–14, 16). Because stimulus–response curves for hyperpnea were readily generated (Figure 1) (6, 11, 13), and because the magnitude of water elimination grew serially, it seems reasonable to anticipate that if the "drying" postulate were correct, the combination of dry inspirates and progressive minute ventilations would have caused the tonicity of the epithelial fluid to rise sequentially in both experiments as the duration of hyperpnea lengthened, and that lung function would directly decrease in proportion to such changes. The expected overall consequence would have been an identical severity of the obstructive response in the two trials, with a minimal effect of temperature *per se*. Clearly, this is not what was observed. The evaporative burdens in both trials were equal in all ways, and the time × intensity products of hyperpnea were matched; yet the severity of the ensuing episodes of bronchial narrowing differed markedly. Cold air produced more airflow limitation than did the warm inspirate, and contrary to expectations, the greatest expenditures of water were associated with the smallest impact on lung function, instead of the converse (Figure 4). Hence, airway desiccation cannot be of major importance, and other mechanisms must be at work.

On first appearance, our data seem to violate long-established principles. Many investigations have shown that as respiratory heat exchange (RHE) rises in asthmatic individuals, the intensity of the airway obstruction follows suit (3–6, 14), but the opposite appears to have occurred in our study. The greatest airway response occurred in association with the smallest W_L and therefore the least heat loss. If the latter is a critical determinant of thermally induced asthma, and if the vaporization of water is an important component of the energy expended during the conditioning of inspired air (3–6), how can such seemingly disparate observations be reconciled? These apparent contradictions are readily explained by examining the homeostatic mechanisms that regulate pulmonary heat flux, and by revisiting the types of experimental protocols previously employed.

The human respiratory tract is designed to save water as efficiently as possible (16–19). Whenever ventilation increases and/or the ambient temperature falls, the temperature of the gas exiting the nose or mouth decreases (16, 17, 19). When hyperpnea and cold air coincide, as they did in our study, the decline in temperature is greater than with either condition alone (Figure 2) (16). Since the temperature of a gas is the prime determinant of the amount of water that it can hold (15), such decrements automatically minimize the quantity of gas exhaled per breath. Thus, although the frigid and warm inspirates produced equal evaporation from the mucosa during inspiration, the cold air resulted in better recovery, with less water being expelled (Figure 3). These features are not unique to our experiment, and have been reported previously in other studies that used similar ventilations and inspired air conditions (6, 20).

The initial study that quantitatively determined the relationship between RHE and airway obstruction in exercise-induced asthma varied the heat content of the air while keeping $\dot{V}_E$ and the duration of hyperpnea constant (6). Under these conditions, an isopleth of RHE at a fixed $\dot{V}_E$ was generated. Others subsequently took a similar approach (3). Because none of these works studied dry air at ambient temperatures or examined the association between RHE and ΔFEV_1 over a series of ventilations, the types of comparisons that can be made between current and previous observations are limited. These difficulties notwithstanding, the available data that can be directly related to ours show excellent concordance. Using the formula for RHE of Deal and colleagues (6), and their revised regression equation to predict the decline in FEV_1 for the given heat loss (21), a decrement in FEV_1 of 14.7% would have been expected during the 4-min frigid air trial air in our study. The actual recorded value was 15.1%. In addition, the RHE–% ΔFEV_1 relationship for the room air trial in our study (i.e., RHE = 1.15 kcal/min, ΔFEV_1 = 10%) falls within 1 SE of the estimate of the regressions of both Deal and associates (21) and Anderson and colleagues (3). Hence, the published findings for the relationship of RHE to airway obstruction in thermally induced asthma have not been transgressed; they have merely been extended to encompass a new set of circumstances.

We do not believe that relying upon measurements of W_L made in the mouth, or assuming that the exhaled air was fully saturated with water vapor, biased our results. The mouth was chosen because all studies thus far performed, including direct measures of heat transfer during hyperpnea in asthmatic and normal subjects, have shown that at least 50% of the water

transferred during the conditioning of inspired air, and subsequently lost to the environment, comes from the intrathoracic airways (7, 8, 17–19). Of this amount, the airways between the trachea and the segmental bronchi account for 15%, and the remainder of the airways represent 35% (7, 8). Hence, a simple correction permits one to localize the site of loss to the extra- and intrathoracic airways with reasonable precision. We felt that attempts at further differentiation would not have been meaningful without direct assessment of the temperatures and water fluxes at specific points in the tracheobronchial tree.

We appreciate that the expired air in our study may not have been fully saturated (22, 23), and that it has been suggested (23) that the movement of water throughout the human respiratory tract may not be a simple distributed process as reported (7, 8, 16). Even if these possibilities are true, however, it is unlikely that they would mitigate our arguments. Typically, the reported deviation from full saturation is small (22), and for this factor to have adversely affected our findings, the water content of the exhaled air in the room air trial would have had to be 50% less than that in the cold trial. There is simply no known precedent for this to occur (16–19). Rather, failure to reach full saturation would have affected both experiments equally, so that only the absolute values of the exhaled water would have been influenced, and not the pattern of events. In the second case, the work in question (23) presents a conceptual model that does not incorporate data that directly reveal the sites of transfer throughout the airways, and its applicability to the present findings is uncertain (7, 8, 13).

Could the results we observed have been due to differences in the site of conditioning in the two trials? Because the water content of inspired air was zero in our studies, and because the levels of hyperpnea were constant in different experiments with each subject, the answer here too appears to be negative. The prime determinants of the depth of penetration of unconditioned air into the intrathoracic airways are the level of ventilation and the temperature and water content of the air (13, 16). For any given temperate-water content profile (save body conditions), the deeper the ventilation, the further into the lungs the inspirate will go before reaching full saturation. Conversely, for any given ventilation, the lower the temperature (and so water content), the higher the gas will go. In the water content–temperature relationship, the enthalpy of the respiratory tract is such that the vaporization of water dominates energy expenditures, and thus governs the position of the isothermal saturation point (6, 20, 24). For example, it takes 0.000304 kcal/L to raise the temperature of air by 1° C, but 0.58 kcal is spent in vaporizing 1 g of water. Thus, although the temperature of the warm inspirate at inspiration was almost 100% greater than that of the cold inspirate, there would, because both inspirates were dry, have been only a 30% difference in the total amount of thermal energy spent to bring them to body conditions (e.g., average cold inspirate: 0.037 kcal/L/min; average warm inspirate: 0.028 kcal/L/min). Such events would have resulted in less than a 1° C difference between the airstream temperatures at the subsegmental bronchi in the cold and warm trials (16). Moreover, any greater penetrance that might have occurred with the cold inspirate would have served to diminish regional water losses (and by inference drying) by spreading them over a greater surface area. Consequently, obstruction should have been attenuated and not amplified.

If airway dehydration is not the cause of exercise-induced asthma, what is? One possibility is thermally induced leakage from the bronchial microcirculation, with edema formation (17, 11, 13). It is now recognized that the airway cooling associated with hyperpnea provokes an increase in bronchial blood flow in humans and other animals, presumably to regulate thermal losses and prevent tissue injury (25–27). In asthmatic individuals this effect is manifested as a rapid resupply of heat (7, 13), which may produce hyperemia and edema of the airway wall by aggravating leakage from a chronically inflamed capillary bed. In any event, it has been conclusively shown by direct measurement that the size of the cooling–rewarming gradient that exists at the end of hyperpnea determines the intensity of the obstructive response (13). The observation that the cold dry inspirate in the present study elicited more bronchial narrowing than did the corresponding warm dry gas confirms the findings in other investigations (2, 12, 20) and offers further support for the vascular theory. At any given ventilation, the minimal heat content of frigid air reduces intrathoracic airstream temperatures more than does warmer air of identical water content (12). Since the depth of cooling directly augments the speed and magnitude of hyperemia (13), this factor could account for our results. It thus seems that the W_L associated with hyperpnea may promote the development of exercise-induced asthma through an effect on the cooling–rewarming gradient rather than through airway desiccation.

***Acknowledgment*:** The authors gratefully acknowledge the thoughtful comments and criticisms of Drs. S. Anderson, E. Daviskas, and A. Freed.

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