Airway Cooling and Rewarming

The Second Reaction Sequence in Exercise-induced Asthma

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Abstract

To determine if a relationship exists among the magnitude and rate of airway rewarming, and the severity of bronchial obstruction in thermally induced asthma, we had seven subjects perform three- to four-point stimulus response curves with isocapnic hyperventilation of frigid air with and without pretreatment with inhaled norepinephrine. The latter was employed to alter the heat supplied to the airway walls by producing vasoconstriction. 1-s forced expiratory volume (FEV_1) was measured before and 5 min after the cessation of each bout of hyperpnea and before and after norepinephrine. On a separate day, the subjects repeated the above challenges while the temperatures of the airstream in the intrathoracic airways were measured. Prenorepinephrine, FEV_1 progressively decreased in a stimulus response fashion as ventilation rose, while norepinephrine shifted this curve to the right. As the level of ventilation increased, the size of the temperature difference between the cooling of hyperpnea and the rewarming of recovery followed suit, and their magnitude was linearly related to the severity of bronchial narrowing. Reducing the mucosal blood supply of the airways with norepinephrine limited rewarming and attenuated the obstructive response. These data demonstrate that the airway narrowing that develops following hyperpnea and the magnitude of the thermal differences are related, and that alterations in blood supply directly affect bronchial heat flux and influence obstruction. (*J. Clin. Invest.* 1992. 90:699–704.) Key words: bronchial circulation • norepinephrine • isocapnic hyperventilation

Introduction

In the past, it has been documented that the initial reaction sequence in the production of airway obstruction in asthmatics after exercise or hyperventilation was linked to the process of respiratory heat exchange and involved a fall in airway temperature (1–7). Recent data have expanded this concept by suggesting that cooling alone is insufficient to produce obstruction, and that a second event, such as the rate of rewarming that occurs in the immediate recovery period, may also be pathogenically important in this condition (8–10). These newer studies have also demonstrated that the airways of asthmatics rewarm more rapidly than normal after hyperventilation and exercise, suggesting the possibility that hyperemia in the walls of the tracheobronchial tree may contribute to the bronchial narrowing seen with these stimuli (9–10).

If the above constructs are correct, it should follow that any event that alters the size of the hyperpnea-recovery temperature differences, the blood supply to the airway walls, or both, should also influence the severity of the airflow limitation that follows exercise or hyperventilation. To test these possibilities, we first determined if varying the degree of airway cooling influenced the obstructive response by altering rewarming. In these experiments, the subjects hyperventilated frigid air at multiple levels of ventilation while pulmonary mechanics and the airstream temperatures within the intrathoracic airways were recorded. We next attempted to change mucosal blood supply by administering a topically active vasoconstrictor aerosol and repeated the hyperventilation challenges. Our observations form the basis of this report.

Methods

Seven atopic asthmatics (six females and one male) with a mean age of 25±2 SEM years served as our subjects. None of them had experienced an upper respiratory tract infection in the 6 wk preceding the study, and none had taken cromolyn or glucocorticoids during this time. Sustained-release bronchodilator preparations were not used by any participant. All refrained from any medication for 12 h before any study day. After giving informed consent, each participant entered a two-part protocol. On day 1, all subjects performed isocapnic hyperventilation at three progressively increasing levels of minute ventilation ($\dot{V}_E$),[1] while inhaling frigid air through a heat exchanger. The water content of the inspirate during hyperpnea was < 1 mgH_2O/liter, which for the purposes of this study was considered to be 0. Recovery took place on room air. The temperature and humidity of the air in the laboratory were measured by standard techniques.

Each bout of hyperpnea lasted 4 min. As in former studies, expired air was directed away from the heat exchanger into a reservoir balloon that was being constantly evacuated at a known rate through a calibrated rotameter (4, 8–10). The subjects were coached so as to respire to keep the balloon filled, and in doing so, their $\dot{V}_E$ could be controlled at any desired level. End-tidal CO_2 concentrations 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 end-tidal CO_2 at eucapnic levels.

Maximum-forced exhalations were performed in triplicate using a waterless spirometer before and 5 min after cessation of each bout of hyperpnea. Before the hyperventilation, the curves with the largest 1-s forced expiratory volume (FEV_1) were chosen for analysis. Postchallenge, the subjects' first efforts were used. This approach was taken to

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1. *Abbreviations used in this paper:* FEV_1, 1-s forced expiratory volume; T, airstream temperature; $\dot{V}_E$, minute ventilation.

minimize any superimposed changes in airway geometry that were induced by the volume history effects of the forced exhalations (11–13). After the third period of hyperpnea, each volunteer inhaled 0.04 mg of norepinephrine from a DeVilbiss nebulizer (14). 10 min later, FEV_1 was remeasured. After this, the participants again constructed stimulus-response curves to hyperpnea using the previous levels of $\dot{V}_E$. A fourth level was added to determine if norepinephrine produced a shift in the curve. Spirometry was measured as before. The specific levels of $\dot{V}_E$ used in this study were individualized for each subject based on his/her sensitivity to hyperpnea with cold air and his/her maximum voluntary ventilation. The levels chosen ensured that each participant would be capable of tolerating the highest level of $\dot{V}_E$ without producing a prohibitive decrement in pulmonary mechanics.

To measure airway temperature during hyperpnea and recovery, we had the subjects return to the laboratory on another occasion to undergo bronchoscopy with insertion of a thermal probe. The nose and throat of each person was anesthetized with 4% lidocaine and a fiberoptic bronchoscope was inserted through the nasopharynx into a subsegmental bronchus of the anterior basilar segment of the right lower lobe. As in our previous studies, the distances from the tip of the nose to the major anatomic landmarks were recorded, and a flexible thermal probe containing multiple small thermistors was inserted into the tracheobronchial tree (9, 10, 15). The technical features of the probe have been reported previously (16, 17). Once the tip of the probe was placed beyond the end of the bronchoscope, the latter was removed. The probe was then withdrawn in small increments until the most distal thermistor showed fluctuations in temperature with a deep breath, confirming its location in an unobstructed bronchus. By knowing the length of the probe, the distance the tip was inserted, and the location of each anatomic landmark relative to the tip of the nose, the position of each thermistor within the tracheobronchial tree could be determined. Minimal anesthesia was used during the procedure and no premedication was administered. The stability of the position of the probe was continuously verified as in former experiments (9, 10, 15). After the probe was in its final position, each subject repeated the identical challenges used on day 1 before and after norepinephrine. The inspiratory and expiratory temperatures of the airstream within the tracheobronchial tree during hyperpnea and recovery were continuously measured with a digital computer.

The study was split into two parts because we did not wish to have the subjects perform forced exhalations with the temperature probe in place. We have used similar experimental designs successfully in the past (9, 10, 15). We have also documented previously that the effects of repetitive bouts of hyperpnea on pulmonary mechanics (10, 14, 18) and airstream temperature (10, 17, 19) are identical when inspired air conditions and $\dot{V}_E$ are held constant.

The data were analyzed by paired *t* tests with the Bonferonni correction (20), one- and two-factor analyses of variance, and linear regression analysis.

Results

The $\dot{V}_E$ and airstream temperature data for each challenge for both study days are shown in Table I. In the prenorepinephrine trials on days 1 and 2 (control), the mean values for the three levels of $\dot{V}_E$ used to construct the stimulus response curves were 20±2, 37±2, and 54±4 liters/min (mean±SEM). In the norepinephrine arms of the protocol, the additional level of $\dot{V}_E$ used was 68±8 liters/min. The temperature of the inspired air during hyperpnea ranged between −15±3 and −20±6°C, while the temperature during recovery varied from 22±2 to 24±1°C. The water content of the inspirate during recovery was 10±1 mg/liter on day 1, and 11±2 mg/liter on day 2. There were no significant differences found for any variable between experiments or between days.

Fig. 1 contains the pulmonary mechanical consequences of hyperpnea. As can be seen, increasing $\dot{V}_E$ produced progressively greater airway obstruction in a stimulus-response fashion. The lowest $\dot{V}_E$ resulted in little bronchial narrowing ($\%\Delta FEV_1$ = 3±3%; P = NS), while the intermediate and highest levels evoked mild to moderately severe obstruction ($\%\Delta FEV_1$ = 10±3.7%, $P < 0.001$; and 21.8±2.8%, $P < 0.001$, respectively).

The intrathoracic thermal profiles during inspiration that were associated with the above challenges are displayed in Fig. 2. These data were taken from the trachea and are representative of the events that transpired throughout the tracheobronchial tree. The data during expiration have a higher absolute value and, as in other studies, show the same pattern of change as inspiration (9, 10). Increasing $\dot{V}_E$ resulted in a progressive

Table I. Challenge Data

Control				Norepinephrine			
Hyperpnea		Recovery		Hyperpnea		Recovery	
$\dot{V}_E$ (liters/m)	T (°C)	T (°C)	WC (mg/liter)	$\dot{V}_E$ (liters/m)	T (°C)	T (°C)	WC (mg/liters)
Day 1							
20±2	−15±3	22±2	10±1	20±2	−20±4	22±2	10±1
37±2	−19±4	22±2	10±1	37±3	−19±4	22±2	10±1
54±4	−17±3	22±2	10±1	54±4	−19±4	22±2	10±1
				68±8	−20±6	22±3	10±1
Day 2							
20±2	−17±2	24±1	11±2	20±2	−17±3	24±1	11±2
37±3	−18±4	24±1	11±2	37±3	−16±3	24±1	11±2
54±4	−16±3	24±1	11±2	54±4	−15±3	24±1	11±2
				68±8	−18±2	24±1	11±2

$\dot{V}_E$, minute ventilation; T, temperature of inspired air; WC, water content of inspired air.

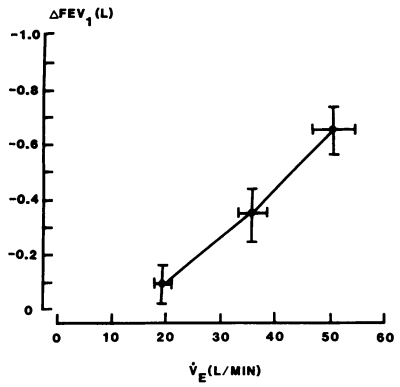

Figure 1. Stimulus-response curve relating ventilation ($\dot{V}_E$) to airway obstruction as measured by change in ΔFEV_1. The data points are mean values, and the brackets are ±1 SEM.

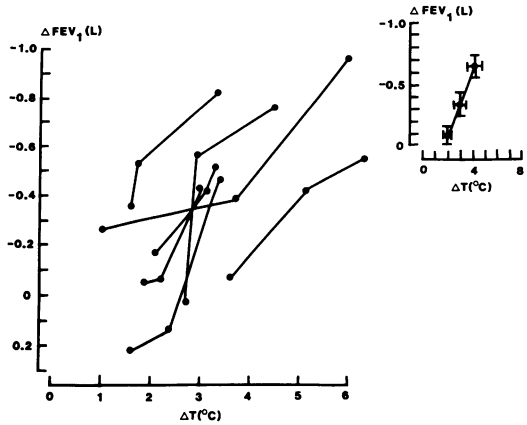

Figure 3. Individual relationships between the changes in temperature (ΔT) that developed 15 s after hyperpnea and the change in ΔFEV_1. In the inset, the data points are mean values, and the brackets are ±1 SEM.

fall in airstream temperatures (T) during hyperpnea. From the highest to the lowest $\dot{V}_E$, T at the end of the last minute of hyperventilation decreased an average of 3°C, from 30.1±0.8 to 27.0±0.6°C ($P < 0.001$). Further, as the airstream temperature fell, both the rate and magnitude of rewarming increased significantly. (ΔT hyperpnea–recovery at 15 s: low $\dot{V}_E$ = 2.1±0.4, med $\dot{V}_E$ = 3.0±0.4, high $\dot{V}_E$ = 4.2±0.5°C; $P < 0.01$. ΔT hyperpnea-recovery at 1 min: low $\dot{V}_E$ = 3.0±0.4, med $\dot{V}_E$ = 4.3±0.6, high $\dot{V}_E$ = 5.5±0.6°C; $P < 0.01$).

The size of the thermal differences between hyperpnea and the initial phase of recovery found at each level of $\dot{V}_E$ was directly related to the degree of obstruction (Fig. 3). These ΔT data were taken 15 s into the recovery period. The data at 30 s show the same pattern. Although there was intersubject variability in sensitivity, each participant showed a stimulus-response relationship between the temperature changes that developed with the cessation of hyperventilation and the severity of their airflow limitation ($r = 0.59$). The larger the temperature differences, individually and as a group (Fig. 3, *inset*), the greater the subsequent bronchial narrowing became.

The administration of norepinephrine (NE) had no effect on pulmonary mechanics. There was no significant difference in FEV_1 before or after the inhalation of this agent (FEV_1 pre-NE = 2.58±0.27 liters, post-NE = 2.70±0.30 liters; P = NS). Norepinephrine, however, did alter the obstructive consequences of hyperpnea and significantly shifted the stimulus-response curve to the right (Fig. 4). Postdrug, $\dot{V}_E$ in excess of 50 liters/min were required to produce significant decrements in FEV_1, and even here the size of the response was less than one half of what it had been predrug ($P < 0.001$). After norepinephrine, $\dot{V}_E$ had to rise to 68±8 liter/min to produce the predrug effect observed at 54±4 liter/min.

The influence of vasoconstriction on the airstream temperatures during hyperpnea and recovery, for the three trials in which there are pre- and postdrug data, are shown in Figs. 5 and 6. In each of these experiments, there were no significant differences for the degree of cooling between the control and the norepinephrine data (min 4: low $\dot{V}_E$ control T = 30.1±0.8°C, post-NE = 30.4±0.8°C, P = NS; high $\dot{V}_E$ control T = 27.0±0.6°C, post-NE = 27.5±0.6°C, P = NS [Fig. 5]). In the recovery phase, however, norepinephrine significantly limited the degree of rewarming that occurred in the first 30 s (Fig. 6): (low $\dot{V}_E$ 30 s control ΔT = 2.6±0.4, post-NE = 2.1±0.2°C, $P < 0.01$; med $\dot{V}_E$ 30 s control ΔT = 3.7±0.5, post-NE = 3.1±0.5°C, $P < 0.01$; high $\dot{V}_E$ 30 s control ΔT = 4.9±0.5, post-NE = 3.8±0.3°C, $P < 0.02$). The temperature differences for the control and postnorepinephrine data for the medium and high $\dot{V}_E$ trials remained significant at 1 min, while those for the low $\dot{V}_E$ did not. By 2 min, no differences between control and norepinephrine existed at any $\dot{V}_E$. During the fourth period of hyperpnea after norepinephrine, ΔT at 15, 30,

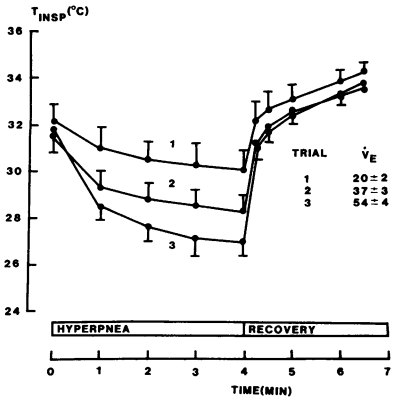

Figure 2. Thermal profiles in the trachea during hyperpnea and recovery at the three levels of ventilation used in the challenges. The data points are mean values for the airstream temperature during inspiration (T insp °C) and the brackets are ±1 SEM.

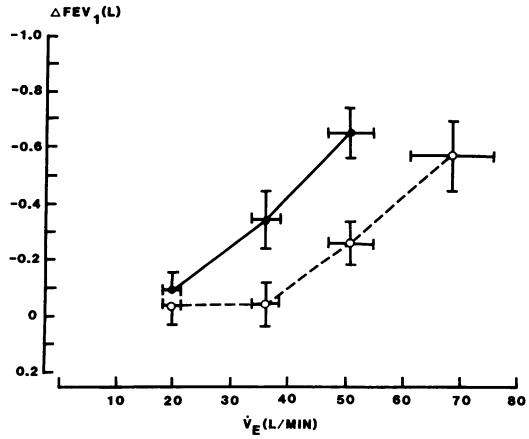

Figure 4. Stimulus dose-response curves relating ventilation ($\dot{V}_E$) to change in ΔFEV_1 with and without norepinephrine pretreatment. The format is identical to Fig. 1. ●, pre-NE; ○, post-NE.

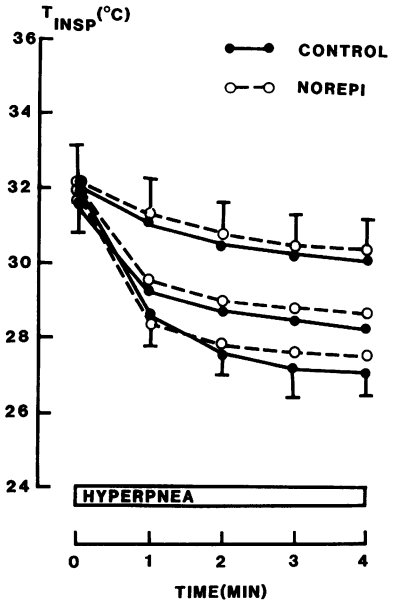

Figure 5. Thermal profiles in the trachea during hyperpnea with and without norepinephrine. The format is identical to Fig. 2.

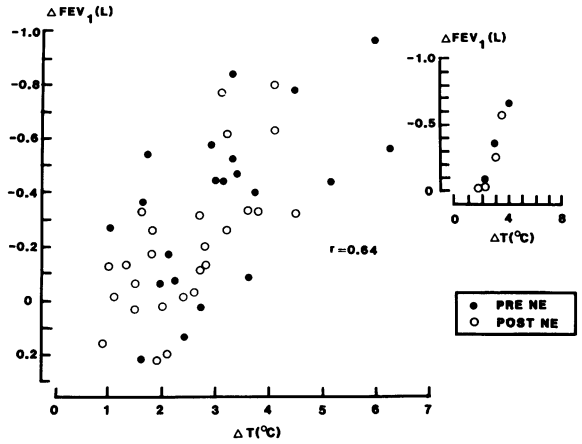

Figure 7. Relationship between the hyperpnea-recovery temperature differences at 15 s after hyperpnea (ΔT), with and without norepinephrine, and the change in ΔFEV_1. The data points are individual values. The inset shows the relationship derived from the mean data.

and 60 s averaged 3.3±0.5, 4.2±0.4, and 5.0±0.4°C, respectively.

The effect of norepinephrine on the individual Δ temperature-obstruction relationship at 15 s is contained in Fig. 7. Norepinephrine reduced ΔT and Δ FEV_1 proportionally so that the original relationship shown in Fig. 3 remained intact. Inclusion or exclusion of the data from the fourth level of hyperpnea after norepinephrine did not alter this relationship (with four levels of $\dot{V}_E$ after norepinephrine $r = 0.64$, with only three levels included, $r = 0.65$). Norepinephrine did not produce a parallel displacement as in Fig. 4. Rather, as the resupply of heat was limited by vasoconstriction, the thermal gradient-obstruction relationship moved along the original prenorepinephrine line (see inset Fig. 7).

Discussion

The results of the present study confirm that both airway cooling and rewarming are essential ingredients in the production of the bronchial narrowing after exercise and hyperventilation. Our data show that the size of the temperature differences that develop in the tracheobronchial tree between the cooling of the final phase of hyperpnea and the rewarming of the initial part of the recovery period play a critical role in thermally induced asthma and directly determine the magnitude of airflow limitation. Small temperature changes are associated with minimal airway narrowing whereas large changes produce symptomatic episodes of asthma (Fig. 3). In addition, our findings also provide insights into the importance of the mucosal blood supply in the development of bronchial narrowing via its linkage to airway rewarming. Reducing mucosal perfusion with norepinephrine diminishes the quantity of heat supplied to the airways during the first minute of the posthyperpnea period, lowers ΔT, and attenuates the obstructive response (Figs. 4–7).

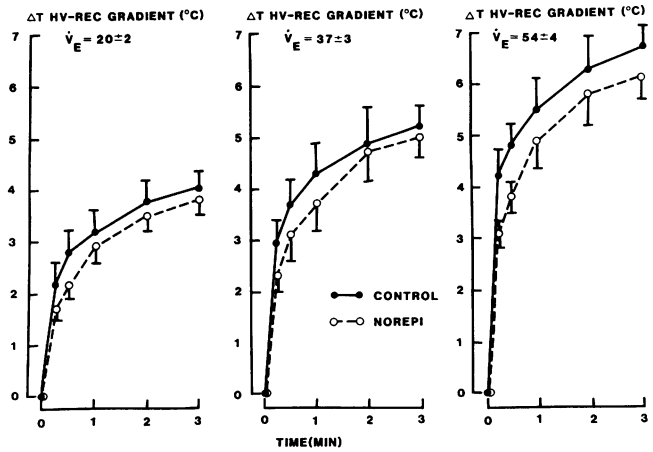

Figure 6. Hyperpnea-recovery temperature differences (ΔT HV-rec) at each level of ventilation with and without norepinephrine. The data points are mean values and the brackets are ±1 SEM.

In composite, the current data unite many observations in the literature on thermally induced asthma and offer direct confirmation of several recent postulates regarding its pathogenesis. Over the last 15 yr, evidence from multiple sources has shown a direct relationship between the quantity of heat lost from the respiratory tract during hyperpnea and the severity of the resulting obstruction (1–7). Small heat losses produced little bronchial narrowing, whereas large losses caused major changes in mechanics. It can now be appreciated that the factors controlling respiratory heat exchange (i.e., inspired air conditions of temperature and humidity and the amount of $\dot{V}_E$) determine not only the level of airway cooling (16, 21, 22), but also the quantity and rate of rewarming (Fig. 2), and through this, the magnitude of airflow limitation (Fig. 4). The lower airstream temperatures fall during hyperpnea, the more the initial rewarming will be and the greater the ensuing obstruction. Conversely, the less the fall, the smaller the temperature difference, and the less the airflow limitation.

Our data also confirm and extend the observations that cooling, per se, is insufficient to produce bronchial narrowing and must be followed by a second reaction associated with a rapid resupply of heat for an acute episode of asthma to develop (8). This resupply phase is quite critical, and if it is interfered with pharmacologically, the obstruction is reduced in proportion to the decrease in recovery temperatures (Figs. 6

and 7). This current data provide direct support of the hypothesis regarding the importance of rewarming that was put forth in previous studies where posthyperpnea temperatures were altered physically by changing the heat content of the inspired air or by controlling $\dot{V}_E$ (8). In these investigations, even though the identical degree of airway cooling was produced by having subjects exercise with the same $\dot{V}_E$ and inspired air conditions, the severity of the resulting bronchial narrowing was amplified or attenuated by increasing or decreasing, respectively, the quantity of heat supplied to the airways immediately postchallenge. Others have reported similar phenomena (23–25).

Is the degree of cooling the only factor that determines the magnitude of rewarming? The answer appears to be no. Since the energy required to reheat the airways following hyperpnea can only come from the circulation, the extent and rate of rewarming appears also to be dependent upon the blood flow to the airway wall. As shown in Fig. 6, when mucosal perfusion is reduced with norepinephrine, the temperatures in the intrathoracic airways do not rise as much as in the control situation even though the amount of hyperpnea induced cooling is statistically identical. This finding with norepinephrine offers direct support for our previous suggestions regarding the potential role of the bronchial circulation in the pathogenesis of thermally induced asthma (8–10). Since we know from earlier work that changes in airstream temperature are reflective of changes in airway perfusion (19), our observations with norepinephrine firmly tie the bronchial circulation to the air flow limitation we produced, for this vascular bed is the primary blood supply to the conducting airways (26).

Norepinephrine is a potent α-agonist with topical vasoconstrictor and decongestant properties whose pharmacology would minimize dilatation and leakage of the affected capillary bed. Although it has a short half-life, its duration of action is approximately three times longer than the length of the experiments herein (27). In addition, the quantity of drug given and the route of administration employed were chosen to produce a local mucosal effect and to exclude a systemic hormonal response (28, 29). Thus, we are confident that the changes in temperature seen after this agent were cause and effect and secondary to a reduction in flow in the bronchial microvasculature rather than because of changes in the pulmonary circulation. Further, since norepinephrine did not influence airway geometry, the shift in the stimulus response curve after this drug must have been caused by a vascular or permeability effect rather than an alteration in bronchial smooth muscle tone.

What is it about rewarming that produces obstruction? Because asthmatics have a hypertrophic and hyperplastic capillary bed in their bronchial walls (30), we have suggested that they may be at risk to develop hyperemia after cooling, either because of purely mechanical effects from a large distended vascular bed (i.e., crowding of the lumen with engorged vessels, and/or increased permeability of the endothelium), or because of abnormal vascular control, or both. Thus far, there are no data either for or against the latter suggestion, and so it remains a possibility. There are, however, several sources of evidence to support that a mechanical effect related to an increase in vascular volume with alterations in capillary permeability is at least playing a role. For example, if thoracic blood volume is rapidly increased at the end of hyperpnea by shifting blood from the legs via antishock trousers, the size of the obstructive response is amplified (30a). Such an effect is also seen with vascular volume expansion with intravenous saline, if it is given at the end of hyperventilation when the vessels are becoming engorged and perhaps leaking (31). Finally, the administration of norepinephrine after the obstruction has developed has been shown to reverse the mechanical defects induced by thermal stimuli (14). Since this agent had no bronchodilator activity in the study under discussion, its beneficial action had to derive from an antiedema and/or vasoconstrictor activity. All of these maneuvers suggest that capillary engorgement with or without edema formation may be quite important pathogenetically. Obviously further experiments will be required before this issue will be completely understood.

Irrespective of mechanisms as to how the temperature differences that we observed induce obstruction, our data also provide insights into how pharmacologic agents interact with the initiating stimuli to produce their protective effects in thermally induced asthma. Various classes of drugs with diverse activities such as α adrenergic agonists (32), α antagonists (33), β-agonists (34), calcium channel blockers (35), and cromolyn sodium (36) eliminate or attenuate the effects of exercise and hyperventilation. In earlier studies, we speculated that these compounds could potentially modulate either the cooling or rewarming phases of the reaction, or both, and so they share a common final pathway involving the vasculature (9). For example, agents with vasodilator activity (α-antagonists, β-agonists, calcium channel blockers, and cromolyn) could all limit the degree of airway cooling, and through this, minimize the amount of rewarming. In contrast, α-agonists would be expected to limit rewarming independently by their vasoconstrictor effects. The current study provides direct evidence that at least some of our concepts are correct, for norepinephrine clearly interferes with the resupply of heat posthyperpnea. This pharmacologic activity of norepinephrine also helps explain why repetitive exercise results in a diminution of the obstructive response in association with an alteration in asthmatics' airstream temperatures (15). Repetitive bouts of work performed in close approximation cause the release of sufficient quantities of norepinephrine into the systemic circulation (37) to allow this agent to function as a circulating hormone (27, 28).

The reason why norepinephrine did not influence the degree of airway cooling is unclear. Based on its pharmacology, one would have expected airstream temperatures to have fallen more than usual during hyperpnea, and they did not. It is possible, however, that the local need to protect the bronchial tissue from the effects of excessive cooling during hyperpnea offset the constrictor effects of this neurotransmitter. Such a phenomenon readily occurs in the digits when their temperatures are lowered excessively (38).

The present data, when coupled with those in the literature, do not support the theory that airway dehydration is the cause of exercise-induced asthma (39). It is now known that the challenges we used do not produce physiologically significant changes in the tonicity of the airway surface fluid, and so airway dehydration does not occur (9, 10, 15). In addition, norepinephrine did not produce bronchodilatation, nor did it influence airway thermodynamics during hyperpnea. Therefore, it is not possible for norepinephrine to have had any effect on regional or global heat and water losses (9, 10, 15). Its protective actions were limited to the recovery period, and had nothing to do with the time in the challenge when dehydration is allegedly developing. Finally, if the osmolarity theory was

correct, the more time spent breathing desiccated air, the more drying and obstruction would be expected, and drugs such as atropine, which reduce the availability of airway water, would worsen the effects of hyperpnea. None of these events occur (8, 18, 23–25, 40).

Acknowledgments

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