

The mechanism of exercise-induced asthma is . . .

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Exercise-induced asthma (EIA) refers to the transient narrowing of the airways that follows vigorous exercise. The mechanism whereby EIA occurs is thought to relate to the consequences of heating and humidifying large volumes of air during exercise. In 1978 airway cooling was identified as an important stimulus for EIA; however, severe EIA also occurred when hot dry air was inspired, and there was no abnormal cooling of the airways. In 1986 the thermal hypothesis proposed that cooling of the airways needed to be followed by rapid rewarming and that these two events caused a vasoconstriction and a reactive hyperemia of the bronchial microcirculation, together with edema of the airway wall, causing the airways to narrow after exercise. The osmotic, or airway-drying, hypothesis developed from 1982-1992 because neither airway cooling nor rewarming appeared to be necessary for EIA to occur. As water is evaporated from the airway surface liquid, it becomes hyperosmolar and provides an osmotic stimulus for water to move from any cell nearby, resulting in cell volume loss. It is proposed that the regulatory volume increase, after cell shrinkage, is the key event resulting in release of inflammatory mediators that cause airway smooth muscle to contract and the airways of asthmatic subjects to narrow. This event may or may not be associated with airway edema. The osmotic and thermal theories come together by considering that inspiration of cold air not only cools the airways but also increases the numbers of airway generations becoming dehydrated in the humidifying process. (J Allergy Clin Immunol 2000;106:453-9.)

Key words: Exercise, airway cooling, airway drying, osmolarity, respiratory water loss

Over the last 15 years there has been considerable debate about the mechanism whereby exercise provokes airway narrowing in asthmatic subjects. There are two major hypotheses: the osmotic hypothesis and the thermal hypothesis.

The *osmotic hypothesis* considers that it is the dehydrating and osmotic effects of water lost, by evaporation in conditioning large volumes of dry air during exercise, that initiate the events leading to contraction of bronchial smooth muscle.¹ This hypothesis considers that the

Abbreviations used

β -Agonist: β_2 -Adrenoceptor agonist
ASL: Airway surface liquid volume
EIA: Exercise-induced asthma
MCC: Measure mucociliary clearance

increase in osmolarity, induced as a consequence of evaporative water loss, provides a favorable environment for the release of mediators from a wide variety of cells and that it is the contraction of the bronchial smooth muscle in response to these mediators that causes the airways to narrow. The narrowing effects of the smooth muscle will be amplified in the presence of airway edema. In addition, the osmotic effects of mucosal dehydration cause an increase in bronchial blood flow during exercise.² Support for this hypothesis has been reported in detail elsewhere.^{2,3}

The *thermal hypothesis* considers that exercise-induced asthma (EIA) is initiated by the thermal effects on the airways caused by exercise, that is, airway cooling during exercise followed by rapid rewarming of the airways after exercise. These thermal effects are proposed to cause a reactive hyperemia of the bronchial microvasculature and edema of the airway wall. The narrowing of the airways is a direct consequence of these vascular events. This hypothesis does not embrace a role for bronchial smooth muscle or inflammatory mediators in the mechanism of EIA. Support for this hypothesis has been reported in detail elsewhere.^{4,5}

The thermal hypothesis, involving the microvasculature, developed from the earlier *airway cooling theory* put forward in 1979.⁶ At that time it was concluded that the "magnitude of EIA is directly proportional to the thermal load placed on the airways and this reaction is quantifiable in terms of respiratory heat exchange" (ie, heat loss).⁶ The osmotic hypothesis was developed and has been sustained because some facts about EIA could not be accounted for by either the airway cooling hypothesis or by its successor, the thermal hypothesis. It is important to the understanding of the current debate of osmotic versus thermal hypotheses to explain some of these facts.

OBSERVATIONS NOT EXPLAINED BY THE AIRWAY COOLING AND THERMAL HYPOTHESES

The most important observation that does not appear to be explained by the airway cooling theory is the doc-

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Supported by the National Health and Medical Research Council of Australia. Received for publication Apr 24, 2000; revised June 26, 2000; accepted for publication June 26, 2000.

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0091-6749/2000 \$12.00 + 0 1/1/109822

doi:10.1067/mai.2000.109822

umentation of quite severe EIA under conditions of inspiring hot dry air.⁶⁻⁹ Further, the percent fall in FEV₁ increased from 32% to 48% by increasing the duration of exercise from 4 to 8 minutes during inspiration of hot dry air.³ This is approximately the same as the increase in severity of EIA from 35% to 48% fall in FEV₁ obtained by cooling the inspired air from +24°C to -10°C.⁶ These findings suggest that both interventions are acting through a mechanism that cannot be explained by equivalent heat loss. Although heat loss will always occur because of evaporation of water, the net heat loss is not always sufficient to cool the airways abnormally during the breathing of hot air. This has been clearly demonstrated by the measurement of a higher expired air temperature during hyperpnea with hot air compared with the temperature measured at rest breathing room air.¹⁰

It appears that water loss is a better predictor of EIA than is heat loss. Hahn et al⁷ found that, when the inspired water concentration was the same, there was no difference in severity of EIA (43% and 48% fall in peak flow) when the inspired air temperature during exercise varied from a cool 9°C to a hot 36°C. Deal et al⁶ also found that the fall in FEV₁ was not significantly different when respiratory water loss during the last minute of exercise remained the same although the temperature varied by 55°C with the only exception being when cold air was inhaled. The water loss in this study was calculated, however, by assuming full saturation of the expired air at the temperature measured, an assumption questioned later by others.¹¹ Eschenbacher and Sheppard¹¹ performed experiments in asthmatic subjects with use of hyperpnea of dry air at -20°C and +39°C. They found technical difficulties with measuring the temperature of expired air when the inspired air was -20°C. These difficulties included freezing of the expired water condensate onto the copper constantan thermocouple during inspiration of cold air. As a result, the response time of the thermocouple dampened very quickly. To overcome this problem, the authors completely separated the inspired and expired airstreams and measured both water and temperature during hyperpnea with cold air. They measured water gravimetrically and found it to be 29.4 mg/L. They found a much higher expired air temperature than had been reported previously for cold air breathing (range 29°C to 33°C, mean 31°C). They concluded that respiratory heat loss was not the sole stimulus for EIA and it was likely that respiratory water loss was also important. These results are important because they suggest that, under cold air conditions, for technical reasons the magnitude of water loss has been underestimated when the expired temperature measurement is depended on to calculate water loss. These technical problems may also explain the low expired air temperature (22°C) and the consequent low water loss calculated during cold air hyperpnea by McFadden et al¹² and the exception of Deal et al⁶ referred to above.

Elegant experiments that clearly reveal the lesser importance of heat loss compared with water loss were reported by Ingenito et al¹³ in 1988 and by Argyros et

al¹⁴ in 1993. Ingenito et al studied the bronchoconstrictor effect brought about by inspiration of cold gases with different volume-heat capacities but the same water-carrying capacity (SF₆O₂ and HeO₂).¹³ Although acknowledging that evaporative water loss must be accompanied by heat loss, these authors found no relationship between temperature gradient and heat loss or between total heat loss and airway response. However, they did find a significant correlation between evaporative water loss and change in lung function. They conclude that the data "provide strong evidence against the hypothesis that total respiratory heat loss is the major provocative stimulus for bronchospasm in this setting." Argyros et al identified three inspired gas conditions that were isenthalpic, that is, they resulted in no net heat loss but did induce mucosal water loss.¹⁴ From their findings, on the fall in FEV₁, they state that "bronchospasm can be induced without significant respiratory heat loss or airway cooling and suggests that it is proportional to the amount of water lost from mucosal surfaces." They conclude "mucosal dehydration as the essential pathophysiologic event for the induction of EIB."

THE CASE AGAINST AIRWAY COOLING AND THE THERMAL HYPOTHESIS OF EIA

In 1986 the airway cooling theory was questioned by the original proponents¹⁵ and revised to the thermal hypothesis that was developed in two major studies.^{4,16} The revision considers that "airway cooling, of itself, was insufficient to produce bronchial narrowing and that rapid rewarming was essential for the obstruction to develop." "If rewarming is prevented or limited, either by having asthmatics inhale frigid gas in the immediate post-hyperpnea period. . . the obstructive response is attenuated."¹⁷ Further, the revised hypothesis also states that "a thermal gradient seems to be necessary at the end of the challenge."¹⁵ The evidence for this conclusion came from a study demonstrating that when rapid rewarming was prevented in asthmatic subjects by having them breathe cold air during controlled recovery the fall in FEV₁ was reduced from 25% to less than 10%.¹⁵

What is apparent from this hypothesis is its failure to explain the earlier findings that EIA severity was greatest when cold air (-10°C) was inspired, both during and for 4 minutes after exercise.⁶ Under the terms of the thermal hypothesis, breathing cold air after exercise should attenuate the response, not enhance it. Further, with hot air breathing during and after exercise, a significant temperature gradient at the end of exercise is clearly not achievable, yet EIA occurs.⁶⁻⁹ The 10 asthmatic adults of Hahn et al⁷ exercised and recovered breathing air at 36°C in an environmental chamber, yet they had a mean fall in peak expiratory flow of 43% ± 18% (SD). In another study a significant temperature gradient is not evident in 20 asthmatic children exercising and recovering, breathing air at 35°C to 40°C and having a mean fall in FEV₁ of 39.8% ± 22% (SD).⁸ These findings are not compatible with the concept that the development of obstruction, under the

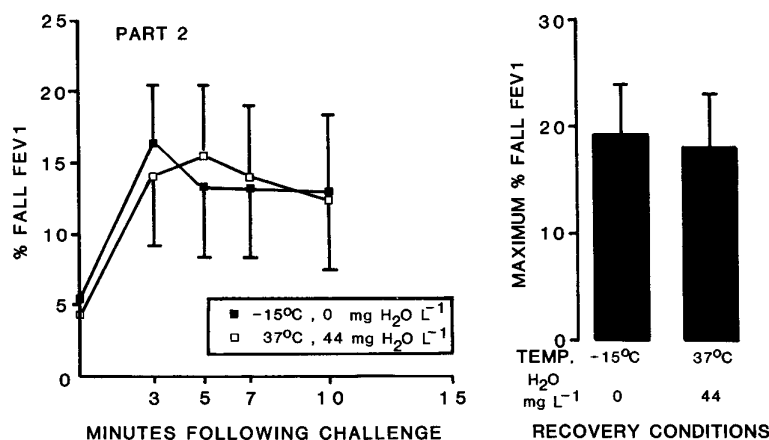


FIG 1. Mean values ($\pm$ SEM) for percentage fall in FEV₁ in relation to time after exercise and the mean maximum percentage fall in FEV₁ in 11 asthmatic boys who performed two exercise tests 4 to 5 hours apart. On both occasions the subjects breathed dry cold air at -15°C . During recovery they either continued to breathe the cold air or they inhaled air at 37°C and $47\text{ mg H}_2\text{O/L}$. There was no significant difference in the airway response during recovery, and no enhancement of EIA was observed when the airways were rapidly rewarmed. These data demonstrate that rapid rewarming of the airways after cold air hyperpnea does not necessarily cause and increase in airway response to exercise. (Reprinted with permission from reference Smith M, Anderson SD, Walsh S, McElrea M. An investigation into the effects of heat and water exchange in the recovery period after exercise in children with asthma. *Am Rev Respir Dis* 1989;140:598-605.)

terms of the thermal hypothesis “appears to consist of vasoconstriction and airway cooling during exercise followed by a rapid resupply of heat when exercise ceases.” Additionally, experiments in children were unable to confirm that the severity of EIA was enhanced even when there was a substantial temperature gradient at the end of exercise and rapid rewarming occurred (Fig 1).¹⁸ Further flow rates can fall during exercise before rewarming occurs¹⁹ and it is not a requirement for all subjects to stop exercising before an attack of asthma begins.

Fundamental to the thermal hypothesis is the assumption that an increase in intra-airway temperature is a reflection of an increase in airway blood flow and that this increase provides a significant source of heat to the airways. Gilbert et al²⁰ report that after hyperpnea the intra-thoracic airways of asthmatic subjects rewarm at twice the rate of healthy subjects and assume that this reflects a reactive hyperemia of the bronchial vasculature. However, this finding could simply be the result of a prolonged residence time of the air in the alveoli as a consequence of air flow limitation in the asthmatic subjects. Further, the bronchial circulation is not a significant source of heat replenishment for the airways²¹ and it represents only 1% of the cardiac output.

Also fundamental to the thermal hypothesis is the concept of vasoconstriction and a reduction in bronchial blood flow because a reactive hyperemia is defined as a consequence of a compromised oxygen supply. Vasoconstriction is an unlikely physiologic response to inhaling hot dry air, and experimental data in both animals²² and man²³ clearly demonstrate that there is an increase in blood flow, rather than a reduction, when dry air is inspired. Recently McFadden et al¹² have acknowledged that bronchial blood flow does increase with dry air

hyperpnea so that a formal revision of the thermal hypothesis has now been made.

The final concept in the thermal hypothesis is that the reactive hyperemia with vascular engorgement and edema of the airway wall are the events that cause an increase in airway resistance and a fall in FEV₁. The concept that resistance can increase as a result of these vascular events alone, however, is not supported by work in animals.²⁴ The thermal hypothesis suggests that the rapid reversal of EIA, in minutes, by β_2 -adrenoceptor agonists (β_2 -agonists) is by vasoconstriction and a reduction in permeability of the bronchial vessels. β_2 -Agonists are not known to be potent vasoconstrictors and their ability to reverse EIA in 5 minutes is more easily explained by their well-recognized bronchodilator effect.

ALTERNATIVE INTERPRETATION FOR INVOLVEMENT OF THE BRONCHIAL CIRCULATION

There is no doubt that the bronchial circulation has the potential to contribute to the pathophysiologic mechanisms of EIA. The bronchial circulation is an important source of water for the airways, and bronchial blood flow increases in response to an increase in osmolarity.²⁵ An increase in bronchial blood flow would not only increase delivery of water to the airways to reduce dehydration and hence the osmotic stimulus but also enhance the clearance of mediators. These two events would be in keeping with the spontaneous recovery in lung function that occurs after EIA. In asthmatic subjects the presence of inflammatory cells and their cytokines makes the concept of microvascular leakage very tenable; this is supported by findings in dogs.²⁶ Hyperosmolarity is known

to cause vasodilation and leakage in animals, which is mediated by nitric oxide,²⁷ the production of which is up-regulated in asthmatic subjects. Edema of the airway wall would serve to amplify the airway narrowing effects of bronchial smooth muscle contraction.

THE CASE FOR WATER LOSS AND THE OSMOTIC HYPOTHESIS

As referred to above, the osmotic hypothesis of EIA¹ arose out of the failure of the airway cooling hypothesis to account for well-established findings on EIA. It was developed after finding that subjects with EIA were also sensitive to aerosols of hypertonic saline solution.²⁸ It was further developed as the marked similarities in the airway response to dry air hyperpnea and hypertonic aerosols became evident.^{29,30}

The osmotic effect of respiratory water loss really came into focus at the time the airway surface liquid (ASL) volume was calculated to be less than 1 mL in the first 10 generations of airways.¹ It is apparent from this calculation^{1,31} that the osmolarity of the ASL can increase rapidly in response to either water loss by evaporation or deposition of hypertonic aerosol particles. The osmotic hypothesis has changed little since 1984 with the epithelial cell involvement in the osmotic change being added in 1989¹⁹ and the submucosal involvement in signaling bronchial blood flow in 1992.² The osmotic hypothesis has been argued^{19,31,32} and sustained because it still serves to explain many of the established facts about EIA. Data have been slowly accumulating to support this hypothesis. It is relevant that there has been only one publication refuting this hypothesis.¹² The potential for these investigators to have underestimated water loss because of technical issues^{11,31} is referred to above.

The experimental evidence used in support of the osmotic hypothesis comes from showing that the severity of the EIA is directly proportional to the water content of the inspired air³³ and to the measured water loss at the mouth.³⁴ When water loss is prevented by inhaling humid air at body conditions, even severe EIA is prevented.^{33,34} However, the magnitude of global water loss measurements at the mouth is not necessarily the same as the local losses from the intrathoracic airways because the mouth provides a significant proportion of the water. For this reason mathematic models were developed to estimate the amount of water that is lost from the lower airways with use of the experimental data and conditions reported by others.^{35,36} The inspired air conditions of +26°C, water content of 8.8 mg/L, and ventilation rate of 60 L/min used in the model are similar to those encountered daily in the laboratory in the summer. Results from the model suggest that only the first 12 generations of airways are needed to humidify the inspired air under these conditions. This model shows that although some airway generations gain water by condensation during expiration, most lose water and there is a net loss of water from the intrathoracic airways. Taking into account this flux and also making an estimate for return of water

to the airway surface, 7.39 mg/L water is calculated to be the net loss from the lower airways during exercise under the conditions described above. This value represents only approximately 25% to 30% of the water loss that is measured at the mouth. Although this value for loss may seem extremely small, relative to the volume of fluid available in the first 12 generations (less than 1 mL),^{1,31} it is relatively large when breathing 60 L/min (ie, $7.39 \times 60 = 0.45$ mL/min). It is not difficult to accept that this rate of water loss from the airway surface liquid is great enough to cause a very rapid increase in its osmolarity. By using this model and by changing the inspired air conditions it is possible to predict that during cold air breathing greater losses of water occur locally in the smaller airways although there is less global loss of water at the mouth.

Where this model extends our thinking is to the realization that there may be significant dehydration of the airway epithelial cells as a result of water moving from them to the airway surface in response to an osmotic gradient. This has been demonstrated for human epithelial cells *in vitro* in response to a hyperosmotic stimulus³⁷ and would appear a valid concept *in vivo* for a number of reasons. First, under normal resting conditions, water is absorbed from the airway surface by the epithelial cells and time may be required for them to switch to being secretory cells.³⁸ Second, animal studies clearly illustrate dehydration of the airway epithelium in response to dry air³⁹ and acute mucosal injury can occur.²⁷ Third, it is known that water replacement to the airway surface is slow because, to prevent inspissation of mucus during mechanical ventilation, the inspired air needs to be humidified although the ventilation is less than 10 L/min. Evidence that the airway mucosa is overwhelmed in its capacity to replenish the ASL comes from the study of Tabka et al⁴⁰ who demonstrate that during exercise breathing warm dry air the expired air desaturates to 80% and the water content falls to 29 mg/L when measured by mass spectrometry. They conclude that the findings are consistent with both dehydration of the airway mucosa and an increase in osmolarity of the airway surface liquid.

In the upper airways Anderson and Togias⁴¹ have reported that the osmolarity of nasal secretions increases with breathing hot dry air. Experiments in dogs demonstrate that dry air breathing results in loss of water from the intrathoracic airways and a significant increase in osmolarity of ASL.⁴² The small volume of ASL spread over a large surface area compromises accurate collection and measurement of fluid and direct measurements of changes in osmolarity in humans during dry air hyperpnea have not been made. Instrumenting the airways increases water flux so that noninvasive techniques to evaluate water loss have been required. One such technique is by measuring mucociliary clearance (MCC). There is now direct evidence that ASL depth is significantly reduced by evaporative water loss in the finding that MCC is markedly reduced by hyperpnea with dry air but not warm humid air (Fig 2).⁴³ After hyperpnea of dry air there is an increase in MCC similar in magnitude to

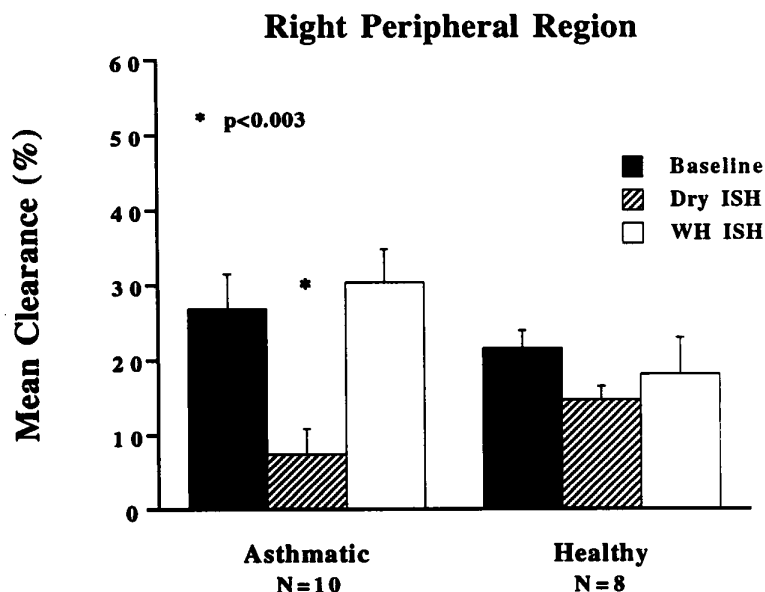


FIG 2. The mean percent clearance ($\pm$ SEM) of the peripheral airways of the right lung during isocapnic hyperventilation (ISH) with dry and warm humid (WH) air and resting nasal breathing (baseline) over the same time interval in asthmatic and healthy subjects. Inhalation of dry air during isocapnic hyperventilation caused a significant reduction ($P = .003$) in mucociliary clearance compared with warm humid air and resting nasal breathing in the asthmatic subjects. There was no difference between mucociliary clearance involving isocapnic hyperventilation with warm humid air and breathing by nose at rest. This demonstrates the possibility that depth of the airway surface liquid is compromised during hyperpnea with dry air. (Reprinted with permission from Daviskas E, Anderson SD, Gonda I, Chan HK, Cook P, Fulton R. Changes in mucociliary clearance during and after isocapnic hyperventilation in asthmatic and healthy subjects. *Eur Respir J* 1995;8:742-51.)

that found with hypertonic aerosols.⁴⁴ This suggests that the ASL is replaced quickly after hyperpnea with dry air in a volume sufficient for MCC, but it is still hyperosmolar. The reduction in MCC occurs in healthy subjects as well as asthmatic subjects although it was not of the same magnitude (Fig 2). These findings have raised the suggestion that asthmatic subjects have a slower rate of transfer of water to the airway surface as a result of airway inflammation.³ An increase in thickness of the basement membrane could explain this finding. The recovery of MCC after hyperpnea with dry air is prolonged with inhaled frusemide.⁴⁵ This finding suggests that ion transport is affecting the regulatory volume increase of the epithelial cell such that the restoration of ASL volume is delayed.

THE MECHANISM FOR WATER LOSS TO CAUSE MEDIATOR RELEASE

The osmotic gradient created in response to the loss of water by evaporation from the airway surface liquid acts as a stimulus for water to move from the surrounding cells to the lumen. As cells lose volume they are subjected to the biochemical events associated with regulatory volume increase. These events include the increase in concentration of intracellular calcium and inositol triphosphate.⁴⁶ These same events are required for the release of media-

tors⁴⁷ and the evidence that an increase in osmolarity does cause release of substances from a wide variety of cells is summarized elsewhere in this issue.⁴⁸

WHAT FACTS ABOUT EIA DOES THE OSMOLARITY HYPOTHESIS ACCOUNT FOR?

If changes in osmolarity caused by water loss lead to the release of mediators, an increase in bronchial blood flow, and bronchoconstriction, it would serve to explain many of the facts about EIA. For example, it would explain why both intensity and duration of exercise are important determinants of severity of EIA. The longer and more intense the exercise, the higher the ventilation rate and the greater the number of generations of airways that will be recruited into the humidifying process. In this way the hyperosmolar stimulus will be spread over a greater surface area and the smaller airways will be recruited into the conditioning process, giving a greater airway response.³¹ This could explain why 8 minutes gives more severe EIA than 4 minutes during hot air breathing. The reason that inspiring cold air can cause EIA in a shorter time than inspiring warm air can¹² can be explained by the more rapid recruitment of the smaller airways into the heating and humidifying process. Thus, when cold air is inhaled, there is the potential for

the smaller airways to lose water quickly, thus creating an osmotic gradient faster than would occur with warm air breathing. The inhibitory effects of histamine and leukotriene receptor antagonists on EIA also support an role for mediator release in EIA, and spontaneous recovery from EIA may occur because these mediators⁴⁸ are rapidly cleared from the airway by the bronchial circulation. Further, the osmotic stimulus will diminish as water delivery to the airways exceeds water loss. The refractoriness of the airways to repeat challenge by exercise may be explained by improved water delivery to the airways provoked by the initial exercise challenge. Increasing delivery of water, no matter how small the volume, will reduce the number of airways involved in the conditioning process. Warm-up with submaximal exercise or multiple sprints may also act to increase bronchial blood flow and enhance water delivery to the airway mucosa. Small increases in water concentration in the inspired air may also serve to protect the smaller airways from being recruited so that EIA is inhibited. This could explain why masks and heat exchange devices are effective although they add only a small amount of water to the inspired air. It also explains why nasal breathing during exercise reduces the severity of EIA.

β -Agonists may not only prevent EIA by their action on bronchial smooth muscle but also in their capacity to increase the rate of water transport to the airway surface by stimulating chloride ion secretion on the apical surface of epithelial cells.³⁸ The inhibitory effects of vasodilators such as the isorbide nitrates and calcium channel blockers could also be explained on the basis of improved water delivery to the airway mucosa.

Fundamental to the osmolality hypothesis is the concept that persons responsive to hyperpnea are also responsive to hypertonic stimuli. This has been clearly shown for asthmatic subjects performing exercise, hyperpnea, and inhaling hypertonic saline solution and mannitol.^{29,30,49} Further drugs that prevent EIA also prevent responses to hypertonic stimuli.^{48,50}

BRINGING THE HYPOTHESES TOGETHER

We conclude that neither abnormal airway cooling nor rapid rewarming of the airways is a prerequisite for EIA and that the thermal hypothesis does not explain many of the facts about EIA, particularly EIA that occurs under hot dry conditions. We agree that airway cooling and rapid rewarming of the airways do occur when cold air is inhaled during exercise, but these events are not necessary for EIA to occur. We suggest that hyperpnea with cold dry air be considered not only for its capacity to cool the airways but also for its potential to involve smaller airways in the humidifying process and, as a result, becoming dehydrated and hyperosmolar. We consider the mechanism for EIA to be due to the dehydrating and osmotic effects of respiratory water loss that lead to mediator release. We propose that regulatory volume increase, after cell shrinkage, is the key event leading to the release of mediators. Potentially, all cells can be sub-

jected to cell volume loss and these include the epithelial cells, the mast cells, the eosinophils, the macrophages, and the sensory nerve cells. The airways are narrowed by contraction of bronchial smooth muscle in response to the mediators and the effect will be amplified in the presence of airway edema.

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