The following is the abstract of the article discussed in the subsequent letter:

Kotaru, Chakradhar, Rana B. Hejal, J. H. Finigan, Albert J. Coreno, Mary E. Skowronski, Lori Brianas, and E. R. McFadden Jr. Desiccation and hypertonicity of the airway surface fluid and thermally induced asthma. J Appl Physiol 94: 227–233, 2003. First published September 13, 2002; 10.1152/japplphysiol.00551.2002.—To determine whether drying and hypertonicity of the airway surface fluid (ASF) are involved in thermally induced asthma, nine subjects performed isocapnic hyperventilation (HV) (minute ventilation 62.2 ± 8.3 l/min) of frigid air (−8.9 ± 3.3°C) while periciliary fluid was collected endoscopically from the trachea. Osmolality was measured by freezing-point depression. The baseline 1-s forced expiratory volume was 73 ± 4% of predicted and fell 26.4% 10 min postchallenge (P < 0.0001). The volume of ASF collected was 11.0 ± 2.2 μl at rest and remained constant during and after HV as the airways narrowed (HV 10.6 ± 1.9, recovery 6.5 ± 1.7 μl; P = 0.18). The osmolality also remained stable throughout (rest 336 ± 16, HV 339 ± 16, and recovery 352 ± 19 mosmol/kgH2O, P = 0.76). These data demonstrate that airway desiccation and hypertonicity of the ASF do not develop during hyperpnea in asthma; therefore, other mechanisms must cause exercise- and hyperventilation-induced airflow limitation.

Airway surface fluid desiccation during isocapnic hyperpnea

To the Editor: We read with great interest the recent article by Kotaru et al. (10), “Desiccation and hypertonicity of the airway surface fluid and thermally induced asthma.” Unfortunately, we must disagree with the authors’ interpretation of their data. Contrary to the authors’ assertions, the reported methodology and resulting data do not prove or disprove the dehydration and hyperosmolarity theory of exercise-induced or thermally induced asthma.

The methodology is potentially flawed in many ways. We provide six examples below.

First, the site of sampling (the trachea) does not address the site of the dehydration and hyperosmolarity of the airways. The relevant site is likely to be the airway epithelium distal to trachea (2). Conditioning of the inspired air at high ventilation rates involves the intrathoracic airways up to generation 12, and significant water losses would occur distal to the trachea (7).

Second, the study data measure osmolarity of airway surface fluid (ASF). Kotaru et al. (10) do not consider that the osmotic stimulus would be far too transient to measure accurately at the airway surface. It is more likely that the increase in osmolarity from evaporative water loss occurs within the epithelial cells (3, 4) and other cells found superficially in the airways and possibly even the airway submucosa (1). Indeed, it is likely that any hyperosmolarity of the ASF would cause water to move instantaneously from adjacent cells or the submucosa in response to the osmotic gradient. The technique used here simply could not be expected to be able to measure changes in osmolarity of the ASF that are sustained only for a short time.

Third, it has previously been documented that mucociliary clearance is reduced during hyperpnea of dry air (5) and that the effect is prolonged in the presence of furosemide (6). The measurement of mucociliary clearance involves all the airways, not just the trachea, and for this reason it is a superior technique to demonstrate transient dehydration of the airway surface. The prolongation of the drying effect by furosemide is presumably due to the drug delaying the transport of water across the basolateral membrane of the airway epithelium. The authors have failed to address these previous reports that provide evidence that dehydration may occur distal to trachea.

Fourth, it is likely that the authors’ (10) technique introduced artifact that precludes critical evaluation of the data. Kotaru et al. report collection of a volume of ASF in excess of that predicted to be underneath the pledget at this generation, suggesting that the pledget itself caused water secretion. It is possible that the results are explained by the technical difficulties encountered by Erjefalt and Persson (9), in which “absorbing discs severely disturb the epithelial-barrier function and sample subepithelial fluid and solutes including macromolecules.” These problems limit the value of the study, and the conclusions drawn by the authors could be misleading to readers. If it had all been that easy to make the technically adequate and correct measurements, it would have been done years ago when there was a real focus on this area of investigation in cystic fibrosis.

Fifth, the dilution of the ASF sample to measure its osmolality dramatically reduces the precision of the final calculated measurement, thus impairing the investigator’s ability to detect important changes in ASF osmolality.

Sixth, even if the methodology used by the investigators (10) was adequate, the resulting data do not support their conclusions. Kotaru et al. have essentially attempted to prove a negative (isocapnic hyperpnea with cold air does not result in desiccation and hypertonicity of airway surface liquid). In actuality, the investigators failed to detect a change in these parameters, which is an important distinction. Kotaru et al. suggest that osmolalities approaching 600 mosmol/kgH2O are required before histamine release. However, Eggleston et al. (8) stated that “significant histamine release was seen above 360 mosmol/kg,” a value equivalent to an increase of 80 mosmol/kgH2O over the baseline osmolality. The authors indicate that the statistical power of their study only allowed them to detect a change of at least 100 mosmol/kgH2O. Thus this study simply does not have the statistical power to support the authors’ conclusions.

In addition, a paradoxical argument is presented in the discussion. Kotaru et al. proposed, “[w]hen water replenishment mechanisms are excessive, the lumen of the nares and lower airways narrow because the ves-
sels respond to unregulated losses with hyperemia and edema formation to prevent thermal damage.” Thus their very proposal for airway narrowing would appear to require excessive dehydration for the vasculature to respond with excessive water replenishment. After all, how can there be water replenishment without first having water loss?

REFERENCES


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REPLY

To the Editor: We thank Dr. Davis et al. for their most recent letter to the editor. Failure to receive one would have raised concerns about the significance of our efforts. In response, we offer the following points.

First, heat and water move solely as a function of the gradients that exist. Temperature maps of the intrathoracic airways during hyperpnea demonstrate that the largest gradients are in the upper trachea and the smallest are in the lung periphery (3, 4, 8, 9). According to standard physical principles, failure to find alterations in ASF volume and tonicity in the region where the largest gradients exist guarantees that greater changes cannot be present downstream where the gradients are smaller. The authors’ penchant for disregarding such principles and ignoring the existence of data that refute their position is rather remarkable. One can hypothesize as much as one wishes, but, eventually, conjecture must give way to appropriate verifiable evidence, and fact must mute rhetoric.

Second, if the osmotic stimulus was too transient for us to measure, it was also too transient for Dr. Davis to measure (2). May we assume that Dr. Davis is withdrawing his paper on this subject because the results are unreliable? Water movement is passive and travels along osmotic gradients; thus the liquid on the top of a dehydrated cell would be pulled into it unless prevented. Furthermore, airway blood flow increases as ventilation rises (5); hence, a continuous source of water is potentially available to the epithelium to keep intercellular tonicity constant during hyperpnea. Why then should the alleged “hypertonicity” develop or continue to exist? If there are any direct data to support the authors’ concepts, they should be provided. These issues were discussed in our paper. We wonder why the authors pretend otherwise?

Third, we did not mean any offense in not citing the authors’ work on mucociliary transport. Our decision was driven by the fact that these papers do not provide any primary information regarding ASF physiology. Many things change ciliary motility, and none was explored or controlled in the authors’ studies.

Fourth, we ask the authors to remember what a “wick” is and how it works. We wrote about all of the potential limitations of our efforts and how they would affect our findings. Perhaps this was missed. Drying and hypertonicity are not features of respiration in either normal or asthmatic people (6, 7). Conceivably, no one performed these studies previously because it was thought that they could not be undertaken.

Fifth, we wish to remind the authors that we carried three different osmolar solutions through the entire analysis as controls. Any impact on accuracy introduced by the measurement technique would have been detected. Perhaps our methods section and Fig. 1 were missed as well.

Sixth, irrespective of the absolute values recorded, there were no changes with hyperpnea in ASF availability or tonicity; yet airway obstruction developed. Such events, therefore, cannot be the root cause of thermally induced asthma. Our study was appropriately powered. We are aware of the statement in the paper by Eggleston et. al. (1); however, we encourage the authors to be a bit more thorough and examine the data in the graphs.

If the authors’ cannot accept our results, why not repeat the study? If they so wish, we would be happy to have them work with us.

REFERENCES

1. Eggleston, PA, Kagey-Sobotka A, Schleimer RP, and Lichtenstein LM. Interaction between hyperosmolar and IgE-medi-


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