Effect of inspired air conditions on exercise-induced bronchoconstriction and urinary CC16 levels in athletes

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Effect of inspired air conditions on exercise-induced bronchoconstriction and urinary CC16 levels in athletes. J Appl Physiol 111: 1059–1065, 2011. First published July 28, 2011; doi:10.1152/japplphysiol.00113.2011.—Injury to the airway epithelium has been proposed as a key susceptibility factor for exercise-induced bronchoconstriction (EIB). Our goals were to establish whether airway epithelial cell injury occurs during EIB in athletes and whether inhalation of warm humid air inhibits this injury. Twenty-one young male athletes (10 with a history of EIB) performed two 8-min exercise tests near maximal aerobic capacity in cold dry (4°C, 37% relative humidity) and warm humid (25°C, 94% relative humidity) air on separate days. Postexercise changes in urinary CC16 were used as a biomarker of airway epithelial cell perturbation and injury. Bronchoconstriction occurred in eight athletes in the cold dry environment and was completely blocked by inhalation of warm humid air [maximal fall in forced expiratory volume in 1 s = 18.1 ± 2.1% (SD) in cold dry air and 1.7 ± 0.8% in warm humid air, P < 0.01]. Exercise caused an increase in urinary excretion of CC16 in all subjects (P < 0.001), but this rise in CC16 was blunted following inhalation of warm humid air [median CC16 increase pre- to postchallenge = 1.91 and 0.35 ng/μmol in cold dry and warm humid air, respectively, in athletes with EIB (P = 0.017) and 1.68 and 0.48 ng/μmol in cold dry and warm humid air, respectively, in athletes without EIB (P = 0.002)]. The results indicate that exercise hyperpnea transiently disrupts the airway epithelium of all athletes (not only in those with EIB) and that inhalation of warm moist air limits airway epithelial cell perturbation and injury.

asthma; airway epithelial injury; Clara cell

EXERCISE-INDUCED BRONCHOCONSTRICTION (EIB) is the transient airway narrowing that occurs shortly after strenuous exercise. EIB is common in individuals with asthma (13) and in otherwise healthy elite athletes (15). The main determinants for EIB are the osmotic and thermal changes as a consequence of respiratory water loss within the airways by high flow rates during exercise (1). Recently, it was proposed that injury to the airway epithelium contributes to the development of EIB (4, 27).

Injury of the distal airway epithelium was originally demonstrated in animals after hyperpnea with dry air (21, 23, 39) and after endurance training (19). Airway epithelial cell injury was also recently observed in asthmatic subjects with EIB (26, 27). In elite swimmers, airway epithelial cell injury was noticed at rest but was not linked to the presence of airway hyperresponsiveness (AHR) to methacholine (11). Further studies conducted in athletes suggest that exercise hyperpnea causes transient disruption of the airway epithelium independently of bronchoconstriction (9, 18, 37).

It has long been established that inhalation of warm humid air can prevent EIB in asthmatic patients (2, 17). In animals, inhalation of warm moist air has also been shown to reduce hyperpnea-induced mucosal damage (23). Whether inhalation of warm humid air reduces hyperpnea-induced airway epithelial cell injury in humans remains unknown. To clarify the relationship between airway epithelial cell injury, ambient exercise conditions, and EIB in athletes, we conducted a randomized crossover study with exercise in cold dry air vs warm humid air. The co-primary end points were lung function response and urinary excretion of Clara cell CC16.

CC16 is a protein with anti-inflammatory function that is secreted by the nonciliated bronchiolar Clara cells predominantly localized in the distal conducting airways (8). From there, it passively diffuses into the bloodstream and then is rapidly cleared by glomerular filtration (28). In conditions where the integrity of the airway epithelium is compromised, “leakage” of CC16 into the bloodstream is increased (6, 7, 12). Recently, we demonstrated that an 8-min period of hyperpnea of dry air causes an increase in urinary excretion of CC16 (9). We wanted to know if this same response occurred with a short bout of high-intensity exercise performed in cold dry air and if warm humid air would inhibit the airway epithelial response and the increase in urinary CC16 concentration in athletes.

METHODS

Subjects

Twenty-one male athletes, aged 20–45 yr, took part in the study. Inclusion criteria are as follows: participants had to be nonsmokers and to train on a regular basis in a sport with a high aerobic component; they had to be free of any chronic medical condition apart from asthma or EIB and of any respiratory infection in the 4 wk preceding the study visits; and their baseline forced expiratory volume...
in 1 s (FEV₁) had to be ≥80% predicted. The protocol was approved by the Grampian Local Research Ethics Committee. All subjects gave their written informed consent before participating in the study.

**Study Design**

All subjects visited the laboratory on three occasions, and 20 (95%) completed the study within 1 mo. Testing took place between July 2008 and April 2009, when the subjects were in training for their respective sport. The first (preliminary) visit included lung function tests, an incremental exercise test to exhaustion, and a skin-prick screening test. The second and third visits included lung function tests, a constant-high-intensity exercise test, and urine collection. The constant-intensity tests were performed between 1400 and 1600, in random order, in warm humid air and cold dry air. All exercise tests were performed in an environmental chamber (Weiss Gallenkamp, Loughborough, UK).

Prior to the study visits, asthma medication was withheld as follows: 8 h for short-acting β₂-agonists (SABA) and inhaled corticosteroids (ICS), 48 h for long-acting β₂-agonists (LABA), and 48 h for antihistamines (20). All subjects were required to abstain from alcohol, caffeine, and vigorous exercise on the days of testing.

**Preliminary visit.** An incremental exercise test was performed to the point of exhaustion to determine the participants’ maximal oxygen uptake (VO₂ max) and maximal aerobic velocity (i.e., last 1-min stage completed in full). The test was performed on a treadmill (PowerJog JX100, PowerSport International, Bridgend, Mid Glamorgan, UK) with a 1% gradient in temperate environment [18°C and 50% relative humidity (RH)], i.e., 7.8 mgH₂O/l]. The test started with a 3-min warm-up at 8 km/h. The speed increment during the test was 0.5 or 1 km/h every minute, depending on the individual’s fitness level. Breath-by-breath pulmonary gas exchange and heart rate (HR) data were monitored continuously. Standard criteria (30) were used to ensure that VO₂ max was reached during the test by all subjects. The incremental test was preceded and followed (at 3, 5, 10, and 15 min) by spirometry.

**Experimental visits.** Subjects were asked to drink a glass of water 1 h before the experimental visit. On arrival, they emptied their bladder and provided a first urine sample. During the visit, subjects were required to drink a volume of water equivalent to 10 ml/kg body mass. Subjects entered the environmental chamber, which was set for the cold dry condition at 4.0 ± 0.0°C and 37.4 ± 1.7% RH (i.e., 2.5 mgH₂O/l) and for the warm humid condition at 24.9 ± 0.0°C and 93.6 ± 0.6% RH (i.e., 21.5 mgH₂O/l). Once in the chamber, the subjects sat inactive for 5 min. Once they were accustomed to the chamber, the subjects performed baseline spirometry maneuvers in triplicate. They then performed a constant-intensity run at 80% of their maximal aerobic velocity for 8 min, with no warm-up. Breath-by-breath pulmonary gas exchange data and HR were measured continuously. Upon completion of the test, the subjects remained in the climate chamber to perform spirometry maneuvers in duplicate at 3, 5, 10, 15, and 20 min. At 30 and 60 min, the subjects emptied their bladder and provided postchallenge urine samples. This was immediately followed by additional spirometry maneuvers.

**Cardiopulmonary Measurements**

During all tests, pulmonary gas exchange and ventilation were measured continuously using a metabolic cart (CPX Ultima, MedGraphics). Data were averaged over 15-s intervals. The metabolic system was calibrated in the climate chamber before the start of each test using a 3-liter syringe and gases of known concentration. Values were corrected for room temperature, barometric pressure, and RH. HR was measured during all tests using short-range radiotelemetry (Polar S610, Polar Electro, Kempele, Finland).

**Lung Function Measurements**

Spirometry was performed on the metabolic unit (CPX Ultima) following the American Thoracic Society/European Respiratory Society recommendations (36). The equations of Quanjer et al. (41) were used for calculation of predicted values. At all pre- and postexercise time points, the best FEV₁ and forced vital capacity (FVC) values of two reproducible maneuvers were kept for analysis. The maximum falls in FVC and FEV₁ were the lowest FVC and FEV₁ recorded after challenge, expressed as a percentage of the baseline value recorded immediately before exercise (20). The area under the FEV₁ time curve (FEV₁-AUC₀–₆₀) was calculated from the percent change from baseline FEV₁ over the 60-min recovery period using the trapezoidal method.

**Group Constitution**

Subjects were assigned to the experimental (EIB⁺) or control (EIB⁻) group according to the postchallenge change in FEV₁ during the test in the cold dry environment. Subjects who demonstrated a ≥10% fall in FEV₁ (20) over two time points were assigned to the EIB⁺ group.

**CC16 Analysis**

Human Clara cell protein ELISA kits (BioVendor, Modrice, Czech Republic) were used for urinary CC16 analysis. The detection limit was 20 pg/ml. To avoid prostatic contamination (5), the first 100 ml were discarded, and only midstream urine samples were kept. All urine samples were analyzed for creatinine, and the results are expressed as nanograms of excreted mediator per micromole of creatinine. CC16 results are presented as peak vs. baseline, with the peak value being the highest value observed at 30 or 60 min after exercise. The area under the CC16 time curve (CC16-AUC₀–₆₀) was calculated from the absolute change from baseline values during the 60-min observation period using the trapezoidal method.

**Atopic Status**

Skin-prick tests were carried out using standardized allergen extracts (ALK, Abello, UK) of house dust mite, timothy grass, cat hair, a three-tree (alder, silver birch, and hazel) mix, and Alternaria alternata and Cladosporium herbarum, together with a positive and a negative control. A positive test result was a reaction with a ≥3-mm diameter wheal.

**Data Analysis**

Group differences between EIB⁺ and EIB⁻ athletes were analyzed using unpaired t-tests or Mann-Whitney tests. For airway and cardiorespiratory responses to exercise, differences between groups and conditions were assessed using repeated-measures ANOVAs. Pairwise comparisons were carried out post hoc using the least significant difference test. FEV₁-AUC₀–₆₀ and CC16-AUC₀–₆₀ and urinary excretion levels of CC16 were not normally distributed. The between-group differences in FEV₁-AUC₀–₆₀, CC16-AUC₀–₆₀, and baseline, peak, and delta urinary CC16 levels were determined using the Mann-Whitney test, and the between-conditions differences were determined using Wilcoxon’s signed-rank test. The time course of CC16 during each study visit was analyzed using Friedman’s repeated-measures ANOVA on ranks followed by Wilcoxon’s test, when appropriate. A two-way χ² analysis was used to compare the distribution of atopy among the different groups. As >20% of data cells had an expected frequency of <5, results were reported as a Fisher’s exact test. Values are means ± SD or medians (interquartile ranges) for data that were not normally distributed. P < 0.05 was adopted for all tests. Statistical calculations were performed using SPSS 17.0 for Windows (SPSS, Chicago, IL).
Baseline lung function was significantly lower in the EIB+ than the EIB− group (Table 1): FEV1 was reduced by 0.54 liter (P < 0.036), and FEV1/FVC was reduced by 6% (P = 0.012). All 8 (100%) EIB+ athletes and 7 (54%) of the 13 EIB− athletes were atopic (P = 0.046).

Urinary CC16 Levels

Urinary excretion of CC16 increased after both constant-intensity runs in EIB+ and EIB− subjects (P < 0.001; Table 2). Inhalation of warm humid air significantly attenuated this increase (P < 0.001; Fig. 1). In 95% of the cases, the peak of CC16 occurred at 30 min postexercise. Furthermore, warm humid air significantly reduced CC16-AUC0–60 in both groups (P < 0.05; Table 2). In the EIB− group, urinary CC16 normalized after 60 min in the warm humid environment, while it remained above baseline at the end of the recovery period in cold dry air (Fig. 2). Baseline CC16 values of EIB+ subjects were higher in warm humid air than cold dry air (P = 0.017) and were higher than baseline values of EIB− subjects in warm humid air (P = 0.008; Table 2).

Airway Response to Exercise Challenges

Postchallenge maximal fall in FEV1 was significantly reduced in warm humid air in both groups (P < 0.001 and P = 0.004 for the EIB+ and EIB−, respectively; Table 2, Fig. 3). None of the EIB+ athletes had a >10% fall in FEV1 in the warm humid environment. The percent protection afforded by warm humid air on the maximum percentage fall in FEV1 to exercise was 87 ± 15%. FEV1-AUC0–60 was reduced in the warm humid environment in the EIB+ athletes (P = 0.012) and remained unchanged in the EIB− athletes (P = 0.248; Table 2).

Inhalation of warm humid air significantly reduced the postchallenge change in lung volume in the EIB+ group (maximal fall in FVC = 7.8 ± 3.3% and 2.0 ± 2.8% in cold dry and warm humid air, respectively, P = 0.003). No difference was noted in FVC in the EIB− group (maximal fall in FVC = 4.3 ± 3.6% and 3.2 ± 3.9% in cold dry and warm humid air, respectively, P = 0.850).

Cardiorespiratory Response During Constant-Intensity Exercise Tests

Oxygen uptake (expressed as % VO2 max) and ventilation rate (expressed in l/min and percent maximal ventilation) were similar in both environmental conditions in the two study

Table 1. Characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>EIB− (n = 13)</th>
<th>EIB+ (n = 8)</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>28 ± 3</td>
<td>31 ± 9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>180 ± 8</td>
<td>177 ± 7</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>80 ± 11</td>
<td>76 ± 11</td>
</tr>
<tr>
<td>Hours training, h/wk</td>
<td>6 ± 2</td>
<td>9 ± 9</td>
</tr>
<tr>
<td>Years of training</td>
<td>8 ± 7</td>
<td>10 ± 6</td>
</tr>
<tr>
<td>Maximal O2 uptake, ml·kg−1·min−1</td>
<td>53.9 ± 6.6</td>
<td>54.3 ± 4.4</td>
</tr>
<tr>
<td>Maximal ventilation, l/min</td>
<td>151 ± 17</td>
<td>138 ± 18</td>
</tr>
<tr>
<td>HRmax, beats/min</td>
<td>184 ± 7</td>
<td>184 ± 7</td>
</tr>
<tr>
<td>80% MAV, km/h</td>
<td>14 ± 1</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>FVC</td>
<td>5.62 ± 0.80</td>
<td>5.37 ± 0.42</td>
</tr>
<tr>
<td>%predicted FEV1, liters</td>
<td>106 ± 12</td>
<td>107 ± 8</td>
</tr>
<tr>
<td>%predicted FEV1</td>
<td>104 ± 9</td>
<td>97 ± 8</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>82 ± 4</td>
<td>76 ± 7*</td>
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</table>

Values are means ± SD. EIB−, athletes without exercise-induced bronchoconstriction (EIB); EIB+, athletes with EIB; HRmax, maximal heart rate; MAV, maximal aerobic velocity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s. Maximal values are those achieved during incremental test to exhaustion. Spirometry data were obtained at rest during screening visit. *Significantly different from EIB− (P < 0.05).

Table 2. Summary of main results

<table>
<thead>
<tr>
<th></th>
<th>Cold dry</th>
<th>Warm humid</th>
<th>Cold dry</th>
<th>Warm humid</th>
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</thead>
<tbody>
<tr>
<td>Baseline FEV1, % predicted</td>
<td>101 ± 8</td>
<td>103 ± 9</td>
<td>94 ± 8*</td>
<td>94 ± 10*</td>
</tr>
<tr>
<td>Maximal fall of FEV1, %</td>
<td>4.6 ± 3.3</td>
<td>1.4 ± 3.8‡</td>
<td>17.7 ± 6.3*</td>
<td>2.1 ± 2.4‡</td>
</tr>
<tr>
<td>FEV1-AUC0–60, %/min</td>
<td>100 (13–156)</td>
<td>37 (0–133)</td>
<td>537 (472–875)*</td>
<td>20 (68–87)‡</td>
</tr>
<tr>
<td>CC16, ng/μmol creatinine</td>
<td>0.074 (0.048–0.177)</td>
<td>0.077 (0.030–0.136)</td>
<td>0.073 (0.058–0.249)</td>
<td>0.207 (0.095–0.494)*‡</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.857 (0.576–3.199)*</td>
<td>0.558 (0.150–1.179)‡‡</td>
<td>1.958 (0.953–5.882)*†</td>
<td>0.729 (0.339–1.225)††‡‡</td>
</tr>
<tr>
<td>Peak</td>
<td>51 (17–96)</td>
<td>19 (7–31)</td>
<td>62 (35–18)</td>
<td>24 (15–51)‡</td>
</tr>
</tbody>
</table>

Values are means ± SD or medians (interquartile ranges). AUC0–60, area under the curve between baseline and 60 min of recovery; CC16, Clara cell protein. *Significantly different from EIB− (P < 0.05). †Significantly different from baseline (P < 0.001). ‡Significantly different from cold dry air (P < 0.05).
groups (Table 3). Tidal volume (VT) was slightly, but significantly \((P < 0.009)\), increased in both groups in cold dry air compared with warm humid air (Table 3). HR (expressed as percent maximal HR) was higher at the end of the exercise test performed in the warm humid environment \((P = 0.001\); Table 3).

**DISCUSSION**

This study shows for the first time in humans that inhalation of warm humid air can attenuate airway epithelial cell perturbations and injury associated with high-intensity exercise. The increase in urinary levels of CC16, our marker for airway epithelial cell perturbation and injury, was blunted after 8 min of heavy exercise in warm humid air compared with cold dry air in EIB\(^+\) and EIB\(^-\) athletes. Disruption to the airway epithelium seems therefore secondary to dehydration stress and appears to be independent of bronchoconstriction.

This study supports previous findings that suggest that strenuous exercise may injure the airway epithelium of athletes (11, 14, 18) and that perturbations to the airway epithelial cells are not exclusive to athletes with EIB (9). We have extended these findings by demonstrating that inhalation of warm humid air can limit injury to the airway epithelium in humans. Reports of a loss of airway epithelial barrier integrity in healthy athletes after \(1\) a 45-min standardized swimming session (14), \(2\) an all-out rowing test over 1,000 m (37), \(3\) half-marathon races (18), and, now, \(4\) an 8-min exercise bout near maximal aerobic capacity suggest that any kind of exercise associated with high ventilatory demand is likely to perturb the airway epithelium.

The rationale for using CC16 in our study was that acute change in CC16 concentration in extrapulmonary fluids was previously shown to be a sensitive marker for a transient loss of airway epithelial barrier integrity (6, 7, 12). Furthermore, since dehydration of the small airways is thought to be an important determinant for severity of EIB in athletes (4), the distal origin of CC16 (8) made it an ideal candidate.

As previously shown in animal (23) and human (9) studies, the perturbations to the airway epithelial barrier induced by hyperpnea seem only transient. In our athletes, CC16 peaked at 30 min of recovery and progressively normalized thereafter. In the warm humid environment, this return to normal was accelerated in the EIB\(^+\) group. This might be due to a faster repair process under conditions of mild injury in individuals presenting an intact baseline bronchial epithelium. Evidence of airway epithelial cell injury has previously been shown at rest in asthmatic patients with EIB (27) and in elite swimmers (the majority of whom had AHR to methacholine) (11). Since the airway epithelium is known to participate in its own repair (10), intact epithelial cells might have helped with a rapid repair in the EIB\(^+\) group.

Our current results are in keeping with some of our previous work that showed a consistent increase in urinary CC16 after 8 min of hyperpnea of dry air in young women (trained and untrained, with and without EIB) (9). Recently, in young male...
runners without EIB, no significant difference in recovery plasma CC16 level was observed after an 8-km run performed in the heat (31°C and 70% RH, i.e., 22.3 mgH2O/l) or in a temperate environment (20°C and 50% RH, i.e., 8.8 mgH2O/l) (25). That cold dry air, rather than the heat, interferes with CC16 levels may come down to the origin of the small protein. CC16 essentially originates from the Clara cells within the distal conducting airways (8) and is thought to be small enough to diffuse into the bloodstream from the airways along a concentration gradient (28). When cold dry air is inhaled at high flow rates (e.g., during vigorous exercise), airways beyond the 12th generation are recruited into the conditioning process, and greater loss of water occurs locally (22). Airway surface fluid hypertonicity may then directly damage the airway mucosa and/or initiate mediator release, which may further contribute to mucosal injury (23). Local losses of water may also give rise to formation of a hypertonic solution covering the mucosa, leading to an opening of the tight junctions of the airway epithelium (29) and facilitating transmembrane leakage of CC16.

CC16 is also believed to control inflammatory events in the airways, particularly by limiting influx of inflammatory cells (16) and inhibiting fibroblast chemotaxis (34). In mice with induced allergic airway inflammation, accumulation of fibrinogen and thrombin on the surface of distal airways has been shown to enhance airway instability and lead to exaggerated airway closure and AHR to methacholine (43). In our study, the airway inflammatory response may therefore have been responsible for the postexercise fall in FEV1 and FVC in EIB⁺ athletes in cold dry air. This finding is consistent with our previous report that dry air hyperpnea triggers an inflammatory response within the airways of EIB⁻ and EIB⁺ athletes but that the response is more severe in EIB⁺ athletes (33).

We cannot be sure that small airway dehydration was the sole factor responsible for the changes in urinary CC16. Airflow-induced epithelial shear stress may also have caused injury or even death of the epithelial cells (38) and favored CC16 leakage into the bloodstream. However, in animals, dry, but not warm air challenge was shown to induce mucosal damage (23). Moreover, if shear stress was the primary determinant of the increased urinary CC16 excretion postexercise, the peak of CC16 should have been of the same magnitude in all our experimental conditions. EIB⁺ athletes should also have presented a higher peak of CC16 than EIB⁻ athletes in cold dry air [compressive stress to the airway epithelium being enhanced during bronchoconstriction (38)]. However, this was not the case. One limitation to this interpretation is that Vt was not perfectly matched during the exercise tests: Vt was slightly, but significantly, lower during the run in warm humid air. In isolated ventilated perfused rat lung, increased Vt ventilation has been shown to stimulate secretion by the Clara cells (35). Because of the small difference in Vt (~150 ml), it is however unlikely that transmural pressure gradients generated in the proximal airways were that different. In asthmatic individuals, changes in breathing pattern did not significantly alter airway constriction response to hyperpnea (31). Therefore, in the context of our work, the effect of Vt was probably only marginal.

Alongside water loss, heat loss is also regarded as an important factor in the development of EIB (24). Inhalation of cold air may have had two important effects in our experiment: 1) because of a greater surface area of the airways being recruited for the air conditioning (1), it may have amplified the dehydration stress to the airways; and 2) it may have caused postexercise reactive hyperemia (24). This, in turn, may have enhanced permeability of the airway vasculature and favored CC16 diffusion into the bloodstream. Unfortunately, CC16 measurement in urine does not allow a differentiation between increased CC16 transport by concentration gradient due to permeability changes and increased production caused by a localized inflammation. Therefore, further work is necessary to determine the respective effect of water and heat loss on Clara cell function and CC16 release during exercise.

Our findings are of particular relevance to winter sport athletes who expose their airways repeatedly to dehydration stress. Respiratory symptoms, AHR, and airway remodeling are common in this category of athletes (32, 42). As clearly demonstrated in dogs (21), repeated hyperpnea causes mucosal injury, airway inflammation, and AHR. In humans, during episodes of hyperpnea, microvascular leak of bulk plasma may also occur 1) to restore the loss of airway surface fluid (4) and
2) to repair the damaged area (40). The consequences of repeated exudation will be to expose the airway smooth muscle to substances that have the potential to regulate its growth and alter its contractile properties (3, 4). In susceptible individuals, repeated epithelial cell injury could therefore be a key factor in the pathogenesis of AHR.

In conclusion, this study has shown that inhalation of warm humid air limits airway epithelial cell perturbations caused by exercise hyperpnea. In the population studied (i.e., young male athletes), perturbation of the airway epithelium measured as CC16 in the urine was unrelated to bronchoconstriction. This finding highlights the potential for exercise, especially when performed at high intensity in cold dry air, to perturb the airway epithelial cells of fit healthy young individuals. Implementation of new strategies to minimize dehydration stress to the airways is therefore required to protect the long-term respiratory health of elite winter athletes.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


