Airway obstruction during exercise and isocapnic hyperventilation in asthmatic subjects

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Airway obstruction during exercise and isocapnic hyperventilation in asthmatic subjects. J. Appl. Physiol. 87(3): 1107-1113, 1999.—We compared pulmonary mechanics measured during long-term exercise (LTX = 20 min) with long-term isocapnic hyperventilation (LTIH = 20 min) in the same asthmatic individuals (n = 6). Peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV1) decreased during LTX (~19.7 and ~22.0%, respectively) and during LTIH (~6.66 and 10.9%, respectively). In contrast, inspiratory pulmonary resistance (Ri) was elevated during LTX (57.6%) but not during LTIH (9.62%). As expected, airway function deteriorated post-LTX and post-LTIH (FEV1 = -30.2 and -21.2%, Ri = 111.8 and 86.5%, respectively). We conclude that the degree of airway obstruction observed during LTIH is of a greater magnitude than that observed during LTX. Both modes of hyperpnea induced similar levels of airway obstruction in the posthyperpnea period. However, the greater airway obstruction during LTX suggests that a different process may be responsible for the changes in airway function during and after the two modes of hyperpnea. This finding raises questions about the equivalency of LTIH and LTX in the study of airway function during exercise-induced asthma.

Methods

Individuals (n = 6 men) with a clinical history of EIA and a positive exercise challenge test, indicated by a reduction in forced expiratory volume in 1 s (FEV1) >10% of the baseline value postexercise, were included. Subjects regularly used an inhaled β2-adrenergic agonist and/or oral theophylline. None of the participants utilized oral steroids or inhaled corticosteroids in their medication regimen. Informed consent was obtained from each individual before participation. This study was approved by the Human Subjects Committee Review Board at the University of Wisconsin-Madison.

Pulmonary function and the maximal exercise test. Vital capacity, FEV1, and inspiratory capacity were determined by using a Collins 13.5-liter water-sealed spirometer (Warren E. Collins, Braintree, MA). Functional residual capacity (FRC) was determined in a Collins body plethysmograph. Total lung capacity (TLC) was determined as the sum of FRC and inspiratory capacity. Pulmonary function tests were performed after antiasthmatic medications were withheld for at least 12 h.

Immediately after pulmonary function tests, a progressive exercise test was performed on a treadmill to determine each subject’s exercise capacity. Each participant started by walking at 4 miles/h (mph) and 0% grade for 3 min as a warm-up. The speed was then increased to 6.0 mph. Every 3 min the speed of the treadmill was increased by 1 mph until the running cadence was satisfactory to the participant. (Note that 1 subject remained at a speed of 4 mph throughout his progressive exercise test, but his treadmill incline level was progressively increased.) From this point the treadmill was maintained at a constant speed, and grade was increased by 2% until a maximal volitional effort was achieved. Maximal oxygen consumption (VO2max) was calculated by using open-circuit expired-gas analysis, as previously described (26). Measurements of expired gas, inspiratory capacity, end-expiratory lung volume (EELV), and inspiratory and expiratory flow rate were made during the last minute of each exercise stage.

Evaluation of pulmonary mechanics. The breathing circuit used to obtain spirometry, ventilation, and pulmonary mechanics data consisted of a Hans Rudolph two-way nonrebreathing valve (model 2700, Hans Rudolph, Kansas City, MO). Matched Hans Rudolph pneumotachographs (model 3813) were used to measure inspired and expired flows. End-tidal gases were sampled at the mouthpiece and ana-
lyzed by a Perkin-Elmer mass spectrometer (model 1100). Signals were relayed at 75 Hz through an analog-to-digital board (Scientific Solutions Labmaster PGH) to a personal computer, where data were kept in files for later analysis. Inspired and expired volumes were calculated by integration of the flow signals. A Validyne transducer (model MP 45–871 Validyne, Northridge, CA, ± 300 cmH2O) connected to polyethylene tubing (PE-200) measured mouth pressure. Esophageal pressure (Pes) was measured with a 10-cm latex balloon, positioned 8–10 cm above the gastroesophageal junction, connected by polyethylene tubing (PE-200) to a Validyne transducer (model MP 45–871, ±200 cmH2O). Transpulmonary pressure (Ptp) was obtained by computer subtraction of mouth pressure from Pes. Inspiratory pulmonary resistance (Rli) was calculated at the volume corresponding to peak inspiratory flow (PIF). The resistive pressure was determined by subtraction of the elastic pressure drop caused by the volume at peak flow from the Pes at peak flow. The resistive pressure was then divided by PIF to determine inspiratory pulmonary resistance. In other words

$$R_{li} = \frac{P_{tp}(PIF) - P_{tp}(EELV) - \nu L}{C_l(dyn)/PIF}$$

where Ptp(PIF) is Ptp measured at PIF, Ptp(EELV) is Ptp measured at EELV, \(\nu L\) is volume above EELV at PIF, and Cldyn is dynamic compliance for each breath (14). By using the mean flow-volume and pressure-volume (F-V and P-V, respectively) loops plotted for each individual at rest, during exercise, and during recovery, ventilatory volume variables and ventilatory timing variables were measured to obtain an estimation of the ventilatory work. This method is described in detail by Otis (25). Flow and pressure signals were verified to be in phase up to 12 Hz.

Esophageal temperature was measured as an index of body core temperature. A nasopharyngeal temperature sensor (Mon-a-therm, size 9-Fr, Mallinckrodt Medical, St. Louis, MO) was inserted through the nares into the esophagus. The position of the temperature probe was 30–35 cm from the nares. The temperature was read from a Mon-a-therm digital display box (model 6500, Mallinckrodt Medical). This system gives a temperature reading that is updated every 4 s. The temperature of the expired air was obtained with similar equipment by using a probe placed at the expired port of the breathing valve. This corresponded to a distance of 5–10 cm from the mouth.

EELV was measured by having individuals perform inspiratory capacity maneuvers during each collection period. To verify that TLC was attained during each inspiratory capacity maneuver, we confirmed that a peak negative Pes similar to that obtained during the inspiratory capacity maneuver at rest was attained. An index of the difficulty of breathing or dyspnea was also obtained at each collection period by having the subject select a number on the Borg rate scale of perceived exertion (10-point category ratio) (21).

Long-term exercise (LTX) session. Subjects were asked to return within 1 wk for LTX at 70%–85% of their personal VO2max. The duration of exercise was 20 min. To ensure that a maximal EIA response would occur postexercise, the subjects withheld their antiasthmatic medications for at least 12 h before each session. Standard measurements of spirometry were obtained to evaluate the status of lung volume and maximal expiratory flows before, during, and after exercise. To obtain the F-V loops used to match ventilation in the long-term isocapnic hyperventilation (LTH) session, 10–20 F-V tidal breaths immediately preceding the inspiratory capacity maneuvers were averaged, thereby providing representative F-V and P-V loops. The individual subject’s average F-V loop or P-V loop was obtained by dividing each tidal volume (VT) into 1% increments. The flow or pressure value for each increment was summed and divided by the total number of averaged breaths to calculate a mean for each volume increment.

Measurements of Rli, spirometry, and ratings of perceived exertion were recorded at rest, at 2, 5, 10, 15, and 20 min of exercise, and at 4 min after exercise. To obtain spirometry, subjects were asked to inspire fully then forcefully exhale for 3–4 s, and maximal F-V curves were analyzed from stored data.

LTH session. The LTH session was conducted within 2 wk of the LTX session. The session involved 20 min with ventilation equal to or higher than the exercise Ve obtained near the end of the LTX session. Participants withheld their antiasthmatic medication for at least 12 h before each session (the same as for the LTX session). Measurements were made and analyzed as in the LTX session: breathing circuit, Pes, Ptp, pulmonary resistance, work of breathing, temperature, EELV, rate of perceived exertion, and spirometry. Subjects were asked to match their averaged Pes-Vt loop obtained during LTX while matching respiratory rate by using a metronome. Their real-time P-V loop was displayed on a storage oscilloscope (Tektronix 5113A, Beaverton, OR) where the averaged Pes-Vt loop from the previous LTX session was displayed and superimposed on the screen. The subject was instructed to match the superimposed loop. In addition, a metronome signaled the desired breathing frequency (inspiration and expiration) and ratio of inspiratory time to total breath time (Ti/Tt). This arrangement allowed us to match VT, frequency, Ti/Tt, Pes excursion, and duration of LTH. Before the start of LTH, resting levels of end-tidal PCO2 (PETO2) were obtained; this level was maintained during LTH by adding CO2 to the inspired gas.

Data analysis. Statistical comparisons within and between the LTX or LTH sessions were made by using repeated-measures ANOVA followed by paired t-tests. All data are shown as means ± SE unless otherwise noted. All statistical tests of significance were set at a P < 0.05 level.

RESULTS

Maximal exercise test session. Subject characteristics are shown in Table 1. Baseline pulmonary function showed that all subjects were within the normal range of predicted values for TLC, vital capacity, and FRC (Table 2). Two subjects had a reduced FEV1 (<80% predicted), and one of them had a lower than predicted FEV1-to-FVC ratio, indicating a mild airflow limitation. None of the subjects had an increased FRC (gas trapping).

LTX session. During the LTX session all subjects showed changes during recovery consistent with EIA, i.e., a fall in both FEV1 and peak expiratory flow (PEF) >10% of the preexercise value. The mean PEF fell 24.2% from the baseline value of 8.7 l/s at rest. FEV1 decreased by 30.2%, whereas mean Rli increased by 111.77%. All preexercise-to-postexercise comparisons were significantly different (P < 0.05) (Figs. 1–3).

To detect changes in airway function during LTX, comparisons between values at 2 (early stage) vs. 20 min (late stage) of exercise were made for PEF, FEV1, and Rli. PEF and FEV1 decreased significantly at the late stages of LTX by −19.7 and −22.0%, respectively (Figs. 1 and 2), whereas Rli showed a significant increase of 57.6% (Fig. 3).

Table 3 displays the ventilatory responses during LTX and LTH. Voice was relatively constant, ranging...
from 74.0 to 86 l/min as O₂ consumption was maintained between 73.0 and 80.0% of (mean = 76.0%) during LTX. The exercise V₉ also remained fairly constant throughout exercise (2.2–2.5 liters), whereas breathing frequency increased from 31.0 breaths/min at minute 2 to 40 breaths/min at minutes 15 and 20. EELV expressed as %TLC remained at its preexercise level of 44% (3.1 liters) early in exercise but by minute 20 had increased significantly to 57% of TLC (4.0 liters). EELV tended to be elevated postexercise when compared with rest (54% of TLC, P = 0.06). End-inspiratory lung volume (EILV) increased significantly from 78% of TLC during early exercise to 89% of TLC at 20 min of exercise. The work of breathing ranged from 181.0 J/min at 2 min to 349.0 J/min at minute 20 (P = 0.02).

LTIH session. Changes in PEF, FEV₁, and R LI pre-LT IH to post-LT IH were −18.5, −21.2, and 86.5%, respectively, indicating similar levels of bronchospasm to those obtained during LTX (Figs. 1–3).

Comparisons between the onset of LT IH (minute 2) and later stages of LT IH (minute 20) showed that PEF (−6.67%) and FEV₁ (−10.9%) decreased significantly but that R LI (9.6%) remained unchanged during the later stages of LT IH.

Table 3 displays the ventilatory responses during LT IH. In contrast to during exercise (during which V E had a tendency to slowly increase) subjects maintained constant target levels of V E during LT IH, ranging from 93.0 to 97.0 l/min. PETCO₂ was maintained at resting levels (4.6%–4.7%). V T also remained constant throughout LT IH (2.6–2.7 liters). Breathing frequency increased to the constant value of 38.0 breaths/min at minute 2 and was constant throughout LT IH. EELV remained at 44% of TLC (3.1 liters) during minute 2 of mimicking, but by minute 20 reached a level to 50% of TLC (3.5 liters). EELV was not increased post-LT IH when compared with rest. EILV increased from 64.0% of TLC at rest to 83.0% of TLC during early LT IH and increased further to 92.0% of TLC at 20 min of LT IH. The work of breathing ranged from 307.0 J/min at minute 2 to 394.0 J/min at minute 20.

LTX session compared with LT IH session (Table 3). The percent changes in PEF, FEV₁, and R LI at 4 min after hyperpnea compared with prehyperpnea were not significantly different between LTX and LT IH (Figs. 1–3). However, the percent changes between minutes 2 and 20 of hyperpnea were different between sessions, indicating that a more intense bronchospasm developed during LTX compared with LT IH.

V E was higher at the initial stages of LT IH, but, by minute 5 of both challenges, this difference was no longer statistically significant between sessions at comparative time points. This reflects the target levels of ventilation presented to the subjects, who attempted to match V E obtained at later stages of LTX. V T was similar at all time points during LT IH compared with LTX. Ti/TT (0.46 ± 0.01 during both LTX and LT IH) and EELV were similar during both sessions. Relative humidity (45 ± 3% for LTX vs. 45 ± 2% for LT IH) and room temperature were also similar during both sessions.

DISCUSSION

This study measured and directly compared pulmonary mechanics in the same asthmatic individuals during LTX and LT IH matched for ventilation. Previous studies that investigated pulmonary responses during isocapnic hyperventilation and exercise cannot
be used to directly compare the two modes of challenge. Blackie and colleagues (6) measured FEV$_1$ in five asthmatic subjects during 16 min of isocapnic hyperventilation and reported no change in FEV$_1$. Although their results are consistent with our data obtained during the first 4 min of LTIH, they did not report data during exercise. Stirling et al. (31) measured pulmonary resistance in three asthmatic subjects during exercise and isocapnic hyperventilation, but their calculations of expiratory pulmonary resistance could have been significantly affected by dynamic compression of the airway. We expanded on both studies by directly measuring inspiratory resistance and spirometry throughout LTX and LTIH. RL$_I$ is an effort-independent parameter and is unaffected by dynamic compression of the airway (32). In addition, we conducted statistical analyses within and between both sessions for the full 20-min duration. Gilbert and colleagues (16) conducted a study utilizing the same asthmatic individuals during exercise and isocapnic hyperventilation of 6-min duration. However, they reported FEV$_1$ values only prehyperpnea and posthyperpnea. No values during the exercise or hyperventilation were given.

Limitations. During LTIH we attempted to replicate several key respiratory parameters found during LTX: VT, respiratory frequency, VE, and Pes swings. Our results indicate that an individual’s breathing frequency, PET$_{CO_2}$, EELV, VT, and Ti/TT were matched but that VE values in the early stages of exercise were not matched. Although VE tended to be higher throughout the LTIH session, this difference was not statistically significant in later stages of hyperpnea. Because it is known that the level of VE is associated with the severity of EIA (2, 20), our higher absolute level of VE during LTIH should have produced a more severe airway obstruction. However, all indexes of airway obstruction showed comparable changes at 4 min post-LTX and 4 min post-LTIH. The difficulty in matching ventilatory parameters during LTX and LTIH has been
reported in a study by Aaron and colleagues (1) in which subjects tended to overbreathe even though careful attempts were made to control $V_e$, respiratory rate, $V_t$, and EELV. Our results followed a similar pattern. However, because we were interested in instigating EIA during LTIH, having subjects exceed their target ventilation assured us that the absence of airway obstruction was not caused by insufficient ventilation. In addition, the nonrebreathing diaphragms prevented blow-by gases from flowing across the expiration port of the breathing valve during LTIH.

Potential mechanisms. Our results imply that different factors could have contributed to the maintenance of airway patency during LTIH compared with LTX. These potential factors include level of ventilation, breathing pattern, body core temperature, airway temperature, water content of expired air, cardiac output, plasma catecholamines, or locally released mediators.

The level of ventilation and water content of the expired air are thought to have the greatest influence on respiratory heat loss (20) because respiratory heat loss is thought to be directly related to the severity of airway obstruction in EIA (8). Our estimated mean respiratory heat loss (1.44 kcal/min) during LTIH was similar to that reported by Deal and colleagues (10), whose subjects experienced slightly greater bronchospasm compared with ours for the same respiratory heat loss. Because of higher total ventilation, respiratory heat loss was higher for LTIH compared with LTX in our subjects, which would lead us to expect more bronchoconstriction, not less. Similarly, because room air relative humidity was similar in the two trials, the airway global water losses should have been similar or greater during LTIH because of the higher $V_e$ achieved.

An increased $V_t$ could be associated with the bronchodilation observed during hyperpnea (6, 18, 19, 23, 31) caused by a reflex inhibition of bronchomotor tone via slowly adapting pulmonary stretch receptors (19, 30) or direct mechanical stretch of airway smooth muscle (14). Then tendency to higher $V_t$ observed during LTIH compared with LTX in our study may thus have inhibited airway obstruction during LTIH until $V_t$ returned to resting levels in the recovery period. This explanation and our data seem to fit well with the concept of lung inflation modulating airway smooth muscle contraction (15, 33). During LTX, EELV continued to increase progressively above rest (>44% of TLC). The EELV achieved was similar during LTX and LTIH (89 and 92% of TLC, respectively); this EELV value was similar to those previously reported for LTX (32). One consequence of breathing at such high lung volumes is increasing the work of breathing. The mean total work of breathing that our asthmatic subjects achieved during LTX and LTIH was higher compared with the level of total ventilatory work achieved, by normal subjects (125 J/min) working at a higher $%\dot{V}O_{2\max}$ (85%) and level of ventilation (120 l/min) (1).

One interpretation of our breathing pattern results is that, early in LTX, airway patency is maintained (less airway obstruction) because of a higher $V_t$ compared with baseline. However, $V_t$ continued to progressively decrease (5 of 6 participants) during LTX concomitantly with the appearance of airway obstruction. Maintaining $V_t$ during LTIH could possibly have prevented airway obstruction. In the recovery period $V_t$ decreased (approaching baseline values), and bronchoconstriction developed after both challenges.

| Table 3. Mean ventilatory response to LTX and LTIH |
| %Vo2max | Rest 2 min | 5 min | 10 min | 15 min | 20 min | Post |
| 8 ± 0.3 | 73 ± 5 | 74 ± 4 | 80 ± 2 | 75 ± 4 | 76 ± 2 | NA |
| PECO2 | 4.5 ± 0.3 | 4.6 ± 0.3 | 4.7 ± 0.3 | 4.6 ± 0.3 | 4.6 ± 0.3 | NA |
| Ve, l/min | 16 ± 2 | 74 ± 66 | 76 ± 5 | 86 ± 7 | 82 ± 7 | 84 ± 7 | 35 ± 4* |
| VT, liters | 19 ± 2 | 93 ± 46 | 96 ± 6 | 97 ± 6 | 94 ± 5 | 94 ± 4 | 35 ± 4 |
| LTX | 1.1 ± 0.13 | 2.4 ± 0.22 | 2.5 ± 0.22 | 2.4 ± 0.24 | 2.2 ± 0.27 | 2.3 ± 0.28 | 2.0 ± 0.25* |
| LTIH | 1.3 ± 0.1 | 2.6 ± 0.21 | 2.7 ± 0.22 | 2.7 ± 0.23 | 2.7 ± 0.22 | 2.7 ± 0.3 | 1.5 ± 0.1 |
| f, breaths/min | 15 ± 1 | 31 ± 3 | 32 ± 3 | 37 ± 4 | 40 ± 4 | 39 ± 5† | 17 ± 1 |
| LTX | 15 ± 2 | 39 ± 4 | 38 ± 4 | 37 ± 4 | 37 ± 4 | 37 ± 4 | 17 ± 2 |
| EELV, %TLC | 44 ± 4 | 43 ± 2 | 50 ± 3 | 51 ± 4 | 52 ± 4 | 57 ± 4† | 54 ± 2 |
| LTX | 45 ± 5 | 44 ± 5 | 46 ± 4 | 51 ± 4 | 50 ± 5 | 50 ± 4 | 50 ± 4 |
| EELV, %TLC | 63 ± 4 | 78 ± 2 | 85 ± 3 | 85 ± 3 | 85 ± 3 | 89 ± 2† | 79 ± 4‡ |
| LTIH | 64 ± 5 | 83 ± 2 | 85 ± 3 | 92 ± 2 | 87 ± 2 | 92 ± 1† | 73 ± 5* |
| WV, J/min | 17 ± 3 | 181 ± 315 | 192 ± 38 | 290 ± 63 | 330 ± 70 | 349 ± 73† | 75 ± 21‡ |
| LTX | 12 ± 1 | 307 ± 396 | 321 ± 38 | 362 ± 25 | 362 ± 61 | 394 ± 31 | 55 ± 11* |
| LTIH | 17 ± 3 | 181 ± 315 | 192 ± 38 | 290 ± 63 | 330 ± 70 | 349 ± 73† | 75 ± 21‡ |

Values are means ± SE for 6 subjects. LTX, long-term exercise; LTIH, long-term isocapnic hyperventilation; Post, after exercise. $PETCO_2$, end-tidal $PCO_2$; TLC, total lung capacity; $Ve$, minute ventilation; $Vt$, tidal volume; $f$, breathing frequency; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; WV, work of breathing. *Statistically significant (within) preexercise vs. postexercise comparisons. P < 0.05. †Statistically significant (within) 2- vs. 20-min comparisons, P < 0.05. ‡Statistically significant pre-LTX to post-LTX %change vs. pre-LTIH vs. post-LTIH %change comparisons, P < 0.05. §Statistically different time point during LTX vs. respective time point during LTIH comparison, P < 0.05.
Esophageal temperature has previously been utilized as an indirect measure of the thermal changes taking place in the airway (9, 17, 27). The upper esophageal probe utilized in the above-referenced studies was positioned ~29–33 cm from the tip of the nares, similar to the position of our temperature probe. At this position (retrotracheal), temperature changes should reflect changes in tracheal mucosal temperature. Because both esophageal and pulmonary tissue intervene between the probe and the airways, the esophageal temperature was probably higher than actual airway temperature and overestimated the amount of warming observed during LTX. However, our observed esophageal temperature strongly indicates a warming (Table 4). The time constant of the thermocouple in contact with the airway mucosa is <100 ms once it has reached the flat portion of the temperature constant curve. The time constant of the thermocouple in air is <1 s for a 0.3°C temperature change on the flat portion of the temperature constant curve. This indicates accurate temperature measurements of changes up to 0.3°C at a breathing frequency of 30 breaths/min (i.e., 0.15°C change at a breathing frequency of 60 breaths/min). Body core temperature steadily increases with exercise and reaches peak values at 15–20 min, depending on the exercise intensity (27). Because asthmatic subjects are believed to have hypertrophied bronchopulmonary vasculature (12) and hyperreactive airways (5), an increase in body temperature may induce an increase in airway mucosal blood flow. This increase in warm blood could cause vascular edema and congestion and therefore produce airway obstruction (8, 10, 20, 22, 28). Increases in esophageal temperature would reflect thermal changes occurring in the esophageal mucosa, which receives blood at body temperature much like the airway mucosa.

A study of direct airway temperature profiles during LTX, LTIH, and recovery is needed to investigate the role of lung temperature in the production of airway obstruction in asthmatic subjects. Plasma catecholamines, CO₂, H⁺ concentration, lactate, and cardiac output are additional potential factors that could affect our findings. Lactate and H⁺ concentration have been eliminated as potentiators of EIA (29). Catecholamine-induced bronchodilation during LTX likely did not occur in our study. Because catecholamines would have been higher during LTX (3, 31) compared with LTIH, the higher RLI during LTX cannot be explained on this basis.

An elevated cardiac output has been implicated in the increase of bronchomotor tone (30). An increased cardiac output would increase pulmonary blood flow and possibly affect airway heat exchange and induce vascular engorgement and pulmonary edema. In a study by Beck and colleagues (4), exercise intensities were alternated between 40 and 60% VO₂max for 36 min in 6-min intervals. At the higher intensity (higher cardiac output), airway obstruction decreased, whereas at the lower intensity (lower cardiac output), airway obstruction increased, arguing against cardiac output playing a significant role in bronchodilation.

There are multiple chemical mediators that likely affect airway function during exercise and cause the bronchoconstriction seen after exercise in asthmatic subjects. Multiple studies have shown that histamine (7, 11) and leukotrienes (13) (both of which are released by mast cells) play a role in postexercise bronchoconstriction. During exercise, it has been shown that release of vagal tone in normal subjects may be responsible for improvement in airway function. However, this has not been shown in asthmatic subjects. There is only indirect evidence suggesting that bronchodilator mediators could play a role in regulating airway tone during exercise. Epinephrine levels increase during exercise (3), but studies in normal individuals suggest that epinephrine has little influence on bronchomotor tone. Furthermore, differences in epinephrine levels between LTX and LTIH could not explain the present results because the bronchodilator influence would most likely be less during LTIH, during which we documented lower RLI compared with LTX. Other bronchodilator mediators include prostaglandin E₂, found in epithelial cells, and nitric oxide, which can be generated by nonadrenergic noncholinergic nerves (30), epithelial cells, or inflammatory cells of the airway.

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Values are means ± SE. Tₑ, expiratory temperature; Tₑs, esophageal temperature.
explain EIA. A description of pulmonary mechanics and analysis of breathing pattern during exercise or hyperventilation can provide a better understanding of EIA pathophysiology. In view of the differences in airflow function encountered during both bouts of hyperventilation, when mechanisms of EIA are being investigated, it is imperative that exercise be utilized as the specific mode of hyperventilation. Further investigation is needed on the role of exercise and isocapnic hyperventilation used interchangeably to induce and study airflow obstruction in individuals with EIA.

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