Role of airway endogenous nitric oxide on lung function during and after exercise in mild asthma

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Suman, Oscar E., and Kenneth C. Beck. Role of airway endogenous nitric oxide on lung function during and after exercise in mild asthma. J Appl Physiol 93: 1932–1938, 2002—We hypothesized that nitric oxide (NO), a known mild bronchodilator that can be released by several cell types within pulmonary airways, might protect airways during exercise in asthmatic subjects. We studied 17 individuals with documented exercise-induced asthma (screening exercise evaluation) on 2 study days: after treatment with inhaled NO synthase inhibitor $\text{N}^\text{G}$-monomethyl-$\text{l}$-arginine (L-NMMA; 2 ml of 25 mg/ml mist) and after treatment with saline vehicle. Pulmonary resistance ($R_L$, esophageal manometry) rose and forced expiratory volume in 1 s fell more after L-NMMA compared with saline treatment, suggesting a bronchoprotective role for NO at baseline. The rise in $R_L$ seen after L-NMMA treatment was nearly completely reversed in early exercise, suggesting a non-NO-mediated bronchodilation. A slow rise in $R_L$ during constant-load exercise and dramatic increase in $R_L$ after exercise were the same on the 2 treatment days, indicating little role for NO in regulating airway function during and after exercise. We conclude that endogenous NO plays little role in regulating airway function during and after exercise in subjects with mild asthma.


METHODS

Subject recruitment. Seventeen individuals (12 women) with a clinical history of EIA were included in a double-blinded, randomized design study. Written informed consent was obtained from all subjects.

The specific conditions and mediators responsible for the deterioration in airway function after exercise are well known (3), although factors controlling airway function during exercise have not been explored in detail. The relative preservation of airway function during incremental or short-duration, constant-load exercise raises the possibility that active bronchodilator mediators might be released during exercise, either by neural or humoral mechanisms, or by possible mechanical influence on airway cells, such as epithelial cells. Potential smooth muscle relaxant mediators that are known to be present in airway tissue include prostaglandins (mainly PGE$_2$) and nitric oxide (NO). Our laboratory has shown in other studies that prostaglandins do not have a major influence on airway smooth muscle during exercise in humans (7) or during hyperventilation in guinea pigs (35). Similarly, NO synthase inhibition has little effect on the changes in airway function during hyperventilation in the guinea pig (33). The bronchodilator role of NO in humans during the hyperpnea of exercise has not been explored. The main hypothesis for this study is that the release of endogenous NO by airway cells is increased because of changes in the cellular environment during exercise and that the extra NO provides a protective influence, masking a slowly developing bronchoconstrictor influence. We, therefore, preselected subjects for bronchospasm responses during an initial exercise challenge. We then measured airway function in subjects before and at multiple time points during and after 15-min constant-load exercise challenges on 2 study days, after administration of either the NO synthase inhibitor $\text{N}^\text{G}$-monomethyl-$\text{l}$-arginine (L-NMMA) or saline vehicle via aerosol. We used constant-load exercise to allow us to evaluate both the initial change in airway function early in exercise and the slow development of bronchoconstriction during exercise (8) with and without treatment with the NO synthase inhibitor.

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(approved by the Institutional Review Board at Mayo Clinic, Rochester, MN) was obtained from each individual before participation. Six subjects who were using inhaled or nasal corticosteroids withheld the drug for at least 2 wk before the initial exercise screening session; thus all subjects had not been exposed to steroid medications within 2 wk of the initial exercise test. None of the subjects was taking oral β-agonists, methylxanthines, or oral corticosteroids. Inhaled β-agonist medication was withheld for 12 h (short acting) or 24 h (long acting) before each visit to the exercise laboratory.

The study design called for an initial incremental exercise test breathing dry air to determine each subject’s maximal exercise capacity and degree of airway responsiveness to exercise, followed by two separate visits to the laboratory for graded, 15-min constant-load exercise bouts after administration of either L-NMMA or its vehicle, normal saline, by nebulizer in a double-blind fashion. The screening exercise test consisted of a 1-min incremental protocol of ∼8–12 min in duration that was performed breathing dry air (6, 8). Only individuals with at least a 12% drop in FEV₁, comparing the lowest FEV₁ after exercise with the largest FEV₁ before or during exercise, were asked to continue with the study.

**Study design and protocol.** Subjects who met the criteria returned to the laboratory for the two additional constant-load exercise sessions at the same time of day as the initial screening test (±1 h) and after withholding medications as noted above and avoiding caffeine or vigorous exertion for 6 h. Spirometry was performed (1), baseline Rₜ was determined after placement of an esophageal balloon (6), and cuff blood pressure and heart rate (6- or 12-lead electrocardiogram) were recorded. Expired NO was measured by using a chemiluminescent NO analyzer (Sievers Instruments, Boulder, CO) calibrated by using a high-precision tank of 100 parts/billion NO. The subject was asked to inspire fully and then to exhale through a small orifice to control expiratory flow at a fixed rate of ∼400 ml/s. Although this flow rate is higher than the current recommendation of the American Thoracic Society (2), it was carefully controlled by using the orifice, allowing us to document the change in exhaled NO before and after drug and during and after the exercise. NO concentration was measured near the end of the exhalation on a clear plateau in NO concentration.

The subject was then given a placebo treatment using a DeVilbiss 646 nebulizer powered by compressed oxygen at 8 l/min and primed with either 2 ml of saline vehicle or 2 ml of 25 mg/ml L-NMMA solution. The solution was prepared by the Pharmacology Department into coded vials, according to manufacturer’s instructions (Cinalfa, Lauferlingen, Switzerland), by mixing powdered material with sterile saline. In this way, both the investigators and the subjects were blinded as to whether placebo or drug was being given on a particular day. The subjects were not able to tell the difference between drug and placebo by taste or any other sensation. Because inhaled L-NMMA is not approved for any clinical purpose by the Food and Drug Administration of the United States, we notified them of our study protocol and obtained an Investigational New Drug permission to complete this study. The dose chosen is the highest dose reported in the literature at the time that we designed this study (37). The subject then breathed the mist for up to 12 min (until the fluid was depleted) while manually activating the nebulizer on inspiration only. Blood pressure measurements were repeated, and, 15 min after nebulization was completed, spirometry, exhaled NO, and Rₜ measurements were obtained to determine any changes produced by the drug alone.

The study design called for incremental constant-load exercise sessions of 15 min each at 25, 50, and 75% of the subject’s maximal power output determined from the initial screening day. All subjects responded with at least a 15% fall in FEV₁ within 15 min of the lowest level of exercise during one of the two visits, and no subject continued to the third exercise level at either visit; thus only the bouts at 25% of maximal power were analyzed for this report. All subjects completed the full 15 min of exercise at this level, independent of any changes in baseline lung function.

During the 15-min constant-load exercise bouts, Rₜ measurements and expired NO were taken every 5 min. Spirometry was not performed during exercise. Spirometry and Rₜ measurements were repeated at 5, 10, and 15 min posthypopnea.

**Pulmonary mechanics.** Techniques for measuring Rₜ during exercise are described in detail elsewhere (6). Flow and volume at the mouth were measured with a screen-type pneumotachograph (model 2700, Hans-Rudolph, St. Louis, MO) with a ±2 cmH₂O differential pressure transducer. The transducer signal was digitized at a rate of 120 s⁻¹, and the flow data were digitally linearized (38) and then integrated to produce the volume signal. The linearization procedure used a lookup table to apply minor correction factors in small ranges of flow. The lookup table was generated for the pneumotachograph and valve setup used in this study and was kept the same for all subjects. The pneumotachograph was calibrated before each study by using a 3-liter air-filled syringe. Integrated volumes were required to be within ±3% of the syringe volume across a range of flows from ∼0.5 to ∼6.0 l/s. The esophageal balloon placement was through the subject’s naris into the esophagus, as described previously (6). Transpulmonary pressure was taken as the difference between esophageal pressure and lateral air pressure at the mouth. Transducers were calibrated before each study. With the use of the flow, volume, and transpulmonary pressure signals, Rₜ was calculated with the technique of Mead and Whittenberger (21) using flows ±2.0 l/s.

**Data analysis.** All raw data files were analyzed by one technician who was blinded to the drug treatment. Valid breaths for Rₜ measurements were determined by visual inspection of pressure-volume and pressure-flow curves for each breath. Data for breaths with irregularities caused by esophageal spasms or irregularities in breathing pattern were excluded from analysis. Reported values for Rₜ at each time point were the average of at least five valid breaths. Plateau values for expired NO were identified by the same technician, again blinded to drug treatment. As pointed out above, exhaled NO was always measured with flow controlled by a small orifice to ∼400 ml/s.

Statistical analysis was performed by using SAS for the personal computer, version 6.03 (28). Data for Rₜ during exercise were analyzed by using linear regression to determine the rate of change in Rₜ with time during exercise in each subject and individual slopes included with other pulmonary function variables in the following analysis. To test the hypothesis that lung function or expired NO changed as a function of drug or phase of exercise, repeated-measures analysis of variance was used with stage of exercise and/or drug as classification variables. For positive analysis of variance results (P < 0.05), paired t-tests were then used to determine significance of fractional changes in Rₜ or spirometry variables caused by drug for the following stages of exercise: change in Rₜ early in exercise compared with either predrug or postdrug baseline, rate of rise in Rₜ during exercise, and change in spirometry or Rₜ variables after exercise.
compared with either predrug or postdrug baseline. Statistical significance was taken at the P < 0.05 level.

RESULTS

Subjects’ characteristics are listed in Table 1. Spirometry was within normal limits (>80% predicted) with the exception of three subjects: one of whom had a mild reduction in both FEV1 and forced vital capacity (61 and 68%, respectively) and the other two who had mildly reduced FEV1 (~77% predicted) but normal forced vital capacity (>95% predicted). Predrug RL values were also near normal and in the range of those in our laboratory’s previous studies involving subjects with mild asthma (6). During the initial maximal exercise evaluation, all subjects attained a maximal heart rate reasonably close to their predicted maximum, reflecting a good effort on the part of all subjects (range 156–200 beats/min, mean 179 beats/min). The maximal work intensity achieved ranged from 110 to 330 W (mean 186 W), reflecting a range of fitness levels. All subjects satisfied entry criteria into the study, experiencing at least a 12% fall in FEV1 within 15 min of achieving the maximal exercise intensity.

Expired NO measurements are shown in Fig. 1. Because of the higher expiratory flows that we used while measuring expired NO, the NO levels of the subjects were lower than those that have been reported at lower flows that are now considered standard (2) in asthmatic subjects. However, we were not using expired NO as a diagnostic or entry criterion to the study but rather as documentation for effective inhibition of NO synthase. There was no difference in NO levels before drug treatment on the 2 study days, but NO levels fell in every subject after treatment with L-NMMA (P < 0.01). The drop in NO at the onset of exercise was significantly less on the L-NMMA vs. saline treatment day, but the increase in NO after exercise was not significantly different on the drug vs. saline day (P > 0.10). Pooling the drug and saline days, the increase in NO early in recovery was 1.78 ± 3.36 parts/billion (n = 32, P < 0.01). These results indicate that the dose of L-NMMA that we delivered was effective in reducing NO production in the airways of our subjects, and this reduced production persisted throughout the exercise tests on the drug treatment day.

The patterns of change in spirometry and RL are shown in Figs. 2 and 3. After administration of saline, FEV1 dropped slightly (−3.6 ± 1.0%, P < 0.01), and RL tended to increase (6.6 ± 6.8%, P > 0.10). In contrast, with L-NMMA, both the increase in RL (81.0 ± 19.0%) and the drop in FEV1 (−14.8 ± 3.0%) were significantly larger compared with the saline treatment, indicating that L-NMMA affected preexercise airway function. The distribution of responses was as follows: four of the subjects experienced <10% change in FEV1, four subjects experienced >30% drop, and the remaining nine subjects had intermediate responses. Because this was a double-blinded study, neither the subject nor laboratory personnel were aware of the type of treatment given when these responses occurred. Thus preexercise responses to L-NMMA were not used as entry or exclusion criteria for the study, and the responses were not used to alter the subsequent protocol.

The significant bronchoconstrictor response to L-NMMA did not prevent us from testing the main hypothesis of the study: that L-NMMA would prevent an improvement in lung function early in exercise and would enhance a slowly developing bronchoconstrictor influence during exercise in people with exercise-induced bronchoconstriction, indicating a protective influence of endogenous NO. Given the bronchoconstric-

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**Table 1. Subject characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>BMI, kg/m²</th>
<th>FVC, liters</th>
<th>FEV₁, %pred</th>
<th>FEV₁, liters</th>
<th>FEV₁, %EIB</th>
<th>RL, cmH₂O l⁻¹ s⁻¹</th>
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<tr>
<td>Mean</td>
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<td>169</td>
<td>24</td>
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<td>91.3</td>
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<td>Minimum</td>
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<td>155</td>
<td>20</td>
<td>3.28</td>
<td>67.9</td>
<td>2.41</td>
<td>61.5</td>
<td>−66</td>
</tr>
<tr>
<td>Maximum</td>
<td>52</td>
<td>191</td>
<td>31</td>
<td>6.57</td>
<td>150</td>
<td>4.45</td>
<td>133</td>
<td>−14</td>
</tr>
</tbody>
</table>

n = 17 subjects (12 women). EIB, %fall in forced expiratory volume in 1 s (FEV₁) after maximal exercise evaluation, breathing dry air (see text); FVC, forced vital capacity; height, standing height; BMI, body mass index [weight (kg)/height² (m²)]; pred, percentage of predicted values, using Ref. 23; RL, pulmonary resistance determined by esophageal manometry (see text).
NO AND AIRWAY FUNCTION DURING EXERCISE

DISCUSSION

The significant finding of this study is that treatment with the NO synthase inhibitor l-NMMA in aerosolized form has no effect on the changes in lung function induced by exercise in subjects with documented EIA. This conclusion applies to events both during and after exercise. We were surprised to see a bronchoconstrictor response to inhaled l-NMMA alone. For the purposes of the present study, the initial bronchoconstriction caused by l-NMMA did not prevent us from testing the main hypothesis of the study: with the higher preexercise $R_t$, on the l-NMMA treatment day, the drop in $R_L$ early in exercise became larger, and the drop in $R_L$ was not prevented by the l-NMMA treatment.

Effect of NO inhibition preexercise. NO is known to have mild bronchodilator action on human airways when administered exogenously (17). However, there is some debate about its role both in normal airways and in asthmatic subjects. Numerous studies demonstrated no change in baseline lung function after NO synthase inhibition in either animals (22, 33, 39) or
tor response to l-NMMA, we analyzed fractional changes in parameter values by comparing them against both predrug and postdrug preexercise baselines.

$R_L$ remained elevated on the l-NMMA day compared with the saline day up to the start of exercise. The drop in $R_L$ early in exercise compared with the preexercise value was significantly larger on the l-NMMA day compared with saline treatment ($P < 0.01$). This early bronchodilator response brought the $R_L$ values for saline vs. l-NMMA treatment closer together, but the absolute $R_L$ value at the first exercise point was still higher on the l-NMMA day compared with the saline treatment day (repeated-measures ANOVA). The rates of rise in $R_L$ during exercise were significantly greater than zero on both the l-NMMA day and saline days ($P < 0.01$), although the rates were not different between days ($P > 0.10$). The increase in $R_L$ after exercise was significantly higher on the l-NMMA day when percent change was expressed relative to predrug ($P < 0.01$) baseline but not when expressed relative to the higher postdrug preexercise baseline ($P > 0.20$).

Changes in spirometry are shown in Fig. 3. The postexercise fractional changes on the l-NMMA vs. saline days were significantly different when predrug baseline was used but, like the $R_L$ changes, were not significant when postdrug preexercise baseline was used in most spirometric variables, with the exception of the forced expiratory flow at 50% of the vital capacity (FEF50) (for FEV1, $P < 0.015$ relative to predrug, $P > 0.32$ relative to preexercise; for FEF50, $P < 0.05$ relative to predrug, $P < 0.02$ relative to preexercise, repeated-measures ANOVA).
Because of the higher preexercise RL value, the drop in some of our subjects. We used relatively low doses of L-NMMA (<1 mg/ml), although the highest dose used was 100 mM (2 ml of 18.8 mg/ml) (37), slightly lower than the dose that we used (2 ml of 25 mg/ml). Despite this lack of effect on baseline lung function, there is some evidence that endogenous NO has some influence on airway function, on the basis of shifts in dose-response curves from histamine, adenosine 5'-monophosphate, and bradykinin challenge studies (19, 26, 27, 36). We do not know why we observed an effect of NO synthase inhibition when Yates and colleagues (37) reported none at a similar dose. It is possible that differences in inhalation pattern used by the subjects might explain the differences, although further work would need to be performed to adequately address that issue. We studied a larger group of asthmatic subjects, and 4 of our 17 subjects were unresponsive to the NO synthase inhibition, so subject selection may have been a factor. The six asthmatic subjects in the Yates et al. study were not being treated with inhaled corticosteroids, whereas six of our subjects were on treatment before participating in our study but withheld the steroids starting 2 wk before entering our study. Although our study was not designed to examine the effects of prior history of inhaled steroid treatment, there was no clear correlation between reaction to L-NMMA and prior treatment with steroids: four of the subjects previously treated with inhaled steroids were unresponsive to L-NMMA at baseline (<10% drop in FEV1), but two of the subjects previously treated with steroids reacted strongly (>30% drop in FEV1).

The mechanism for the change in baseline lung function is unknown. The primary mechanism is that a drop in NO production by airways reduces a tonic bronchodilator in airway nerves, on airway smooth muscle, or on other cells releasing secondary mediators, such as acetylcholine, histamine, or leukotrienes, are possible. Furthermore, a secondary action caused by a different pH, osmolarity, or other physicochemical property of the L-NMMA solution might occur. The initial pH and osmolarity of the L-NMMA solution that we used were 6.91 and 458 mosM, respectively. After 12 min of nebulization (our maximal amount of time for nebulization), the pH and osmolarity increased to 7.12 and 570 mosM, respectively. These osmolarities are unlikely to have caused changes in airway function. Standard osmotic challenge studies begin with four times normal saline, which has an osmotic pressure >1,200 mosM (4, 14, 29). Further work is necessary to sort out these differences in responsiveness and the mechanism for the bronchoconstriction experienced by some of our subjects.

Effect of NO inhibition during and after exercise. Because of the higher preexercise RL value, the drop in RL early in exercise was larger after L-NMMA treatment, bringing the RL values closer together during exercise. Thus, during exercise, there was a small parallel shift up in the RL values on the L-NMMA treatment compared with the saline treatment day, but the rate of rise in RL was the same. The significant slow rise in RL during hyperpnea is consistent with our laboratory’s earlier studies in both humans (8, 34) and guinea pigs (33, 35), which showed that airway function deteriorates slowly during hyperpnea of constant-load exercise or isocapnic hyperventilation. That inhaled L-NMMA did not prevent the drop in RL early in exercise indicates that the fall in RL was not caused by an increase in endogenous NO production in airways at the onset of hyperpnea. Similarly, the equivalent rate of rise in RL between saline and inhaled L-NMMA treatment indicates that endogenous NO in airways is not playing a protective role later in constant-load exercise. When referenced to predose baseline, the rise in RL and fall in FEV1 preexercise were significantly higher on the L-NMMA treatment day compared with placebo. This is consistent with recent data indicating that NO synthase inhibition causes increased sensitivity in people with mild asthma to isocapnic hyperventilation (19). However, when referenced to the post-treatment baseline, the postexercise fractional changes were not significantly different between placebo and L-NMMA, consistent with the data of study of EIA by De Gouw and colleagues (13). This pattern of results suggests that endogenous NO in airways exerts a tonic dilator influence in subjects with mild clinical asthma and positive EIA tests, but the level of protection is not affected by the hyperpnea of exercise.

It is remotely possible that the drop in RL early in exercise could be due to NO derived from nonairway sources that would not be blocked by L-NMMA administered to the airways. Such sources of NO might include pulmonary endothelium or blood-borne NO from other vascular beds. We think this possibility is unlikely because of the high avidity of hemoglobin for blood-borne NO (15, 17), which would render the concentration of NO in alveolar gas from either other vascular beds or the pulmonary endothelium to be very low. It has been shown that exhaled NO is not markedly affected by changes in pulmonary blood flow in animal studies (23), and modeling studies suggest that the contribution of nonairway sources to exhaled NO is negligible (15, 17). Thus NO concentration in the airway wall from these sources would likely be extremely low.

In asthmatic subjects, airway function is relatively well preserved during hyperpnea of exercise, especially compared with the often dramatic drop in airway function that frequently occurs shortly after exercise stops, implying a relatively potent bronchodilator influence operating during the hyperpnea. The bronchodilator action is also short-acting, as airway function varies with level of exercise when intensity is varied (7, 8). There are only a few known endogenous bronchodilator agents that could be effecting this change. Blocking prostaglandin production has no effect on this change in either guinea pigs (35) or humans (7). Calcitonin gene-related peptide coexists with neurokinins in sensory nerve endings and might play a bronchodilatory role in regulating airway function in guinea pigs (25);
however, it has not been detected in human airway nerve endings, so its role in human asthma is a matter of debate (11). Plasma catecholamines, which could exert a bronchodilator effect, rise during exercise (9) and fall abruptly after exercise (5), a pattern that would be appropriate for bronchoprotection during exercise that dies away soon after cessation of exercise, permitting bronchoconstriction to occur. Because circulating catecholamines do not rise during hyperventilation (5), our laboratory's previous finding that R.I. is, if anything, slightly higher during exercise compared with hyperventilation (34) suggests that the circulating catecholamines during exercise must not have a significant effect on airway function. Consistent with this, β-blockade with intravenous propranolol caused slight preexercise bronchoconstriction and more severe postexercise bronchoconstriction, but did not alter the early bronchodilation seen during exercise in children (31).

Mechanical effects of tidal ventilation could have bronchialolytic influence. Because of interdependence, the increase in lung volume excursion secondary to increased tidal volume of exercise might increase the degree of mechanical stretch imposed on airway smooth muscle. In vitro, it has been shown that tidal stretches inhibit smooth muscle activity (16). Although some studies suggested that reduced mechanical interaction between lung parenchyma and airway smooth muscle was a major defect in asthma (30), studies of airway mechanics in asthmatic and control subjects indicate that mechanical coupling is intact in airways as small as 1–3 mm in diameter (10). Furthermore, a recent study by Crimi and colleagues (12) strongly suggests a mechanical influence that preserves airway function during exercise, even when airway function is reduced before the exercise begins, as in our study. Thus, given our negative results of both NO synthase inhibition in the present study and cyclooxygenase inhibition (7), a bronchodilator effect of increased tidal stretch on smooth muscle becomes the most attractive hypothesis for a protective mechanism that prevents airway narrowing during exercise in individuals with EIA.

The lack of a significant effect of L-NMMA on airway function during exercise is unlikely related to technical factors or study design. We used both spirometry and R.I. measurements to document changes in lung function before and after exercise, and both measures gave a consistent story: there was no difference in the bronchoconstriction that occurs after exercise on the saline treatment vs. the L-NMMA treatment day when postexercise values were compared with immediate preexercise (post-L-NMMA or saline) values, but there was a larger drop in lung function after exercise when fractional changes were computed relative to predrug baseline. We used R.I. measurements to document changes in lung function during exercise. This measure of lung function has the advantage that it does not require any special maneuvers on the part of the subject. Because changes in flows or lung volume during exercise have only a minor influence on R.I. measures (6), R.I. reflects the state of the lung mechanics at the time of acquisition, unaffected by special maneuvers such as deep inspirations.

In conclusion, we found that administration of the NO synthase inhibitor L-NMMA to individuals with known EIA did not prevent the relative protection of airway function by exercise. Furthermore, treatment with L-NMMA did not alter the slowly developing bronchoconstriction that develops during constant-load exercise, and it did not alter the larger bronchoconstriction that occurs after exercise, after controlling for the bronchoconstrictor effect of the drug at baseline. These results suggest that endogenous NO release may exert a bronchodilator influence under normal conditions in subjects with mild asthma, but NO does not play any additional role in regulating airway function during or after exercise.

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