Role of nitric oxide in the airway response to exercise in healthy and asthmatic subjects

H. W. F. M. DE GOUW, S. J. MARSHALL-PARTRIDGE, H. VAN DER VEEN, J. G. VAN DEN AARDWEG, P. S. HIEMSTRA, and P. J. STERK. Role of nitric oxide in the airway response to exercise in healthy and asthmatic subjects. J Appl Physiol 90: 586–592, 2001.—A role of nitric oxide (NO) has been suggested in the airway response to exercise. However, it is unclear whether NO may act as a protective or a stimulatory factor. Therefore, we examined the role of NO in the airway response to exercise by using N-monomethyl-L-arginine (L-NMMA, an NO synthase inhibitor), L-arginine (the NO synthase substrate), or placebo as pretreatment to exercise challenge in 12 healthy nonsmoking, atopic asthmatic patients in a double-blind, crossover study. Fifteen minutes after inhalation of L-NMMA (10 mg), L-arginine (375 mg), or placebo, standardized bicycle ergometry was performed for 6 min using dry air, while ventilation was kept constant. The forced expiratory volume in 1-s response was expressed as area under the time-response curve (AUC) over 30 min. In healthy subjects, there was no significant change in AUC between L-NMMA and placebo treatment [28.6 ± 17.0 and 1.3 ± 20.4 (SE) for placebo and L-NMMA, respectively, P = 0.2]. In the asthmatic group, L-NMMA and L-arginine induced significant changes in exhaled NO (P < 0.01) but had no significant effect on AUC compared with placebo (geometric mean ± SE: −204.3 ± 1.5, −186.9 ± 1.4, and −318.1 ± 1.2%·h for placebo, L-NMMA, and L-arginine, respectively, P > 0.2). However, there was a borderline significant difference in AUC between L-NMMA and L-arginine treatment (P = 0.052). We conclude that modulation of NO synthesis has no effect on the airway response to exercise in healthy subjects but that NO synthesis inhibition slightly attenuates exercise-induced bronchoconstriction compared with NO synthase substrate supplementation in asthma. These data suggest that the net effect of endogenous NO is not inhibitory during exercise-induced bronchoconstriction in asthma.

exercise-induced bronchoconstriction; vascular leakage; exhaled nitric oxide

NITRIC OXIDE (NO) is a small radical that is formed during the conversion of the amino acid L-arginine to L-citrulline by NO synthases (NOS) (30). Two functionally different NOS isoforms have been described. Constitutive NO synthase (NOS) is constitutively expressed in particularly endothelial and neuronal cells and may be activated after increases in intracellular calcium. In contrast, the expression of inducible NOS can be induced by proinflammatory cytokines in epithelial and several inflammatory cells within the airways (23, 38).

During the past few years, evidence has been accumulating that NO may play a role in asthma pathophysiology (5). Endogenous NO can be measured in the exhaled air and is increased in patients with asthma (5). A further increase in exhaled NO has been demonstrated after allergen exposure (21) or respiratory viral infections (12), whereas inhaled steroid treatment has been shown to reduce those levels of exhaled NO (22). Recently, several studies have demonstrated that endogenous NO release, as measured in exhaled air, is increased during exercise in healthy subjects (9, 33, 34). This increase may be due to increased NO production or increased NO release into exhaled air (16, 19) or might be the consequence of a reduction in NO uptake by, e.g., oxyhemoglobin, as a result of increased flow rates during exercise (41).

Exercise provokes bronchoconstriction in 70–80% of patients with asthma (2). The major trigger for the induction of the exercise response seems to be the drying and cooling of the airways due to the ventilatory stimulus (10), which may elicit obstruction of the airways by contraction of bronchial smooth muscle, vasoconstriction, and edema (2). In normal subjects and asthmatic patients, bronchodilation occurs during the first few minutes of exercise (3). In asthma, such an increase in forced expiratory volume in 1 s (FEV1) is inversely correlated with baseline values; i.e., the patients with the greatest level of preexisting airway obstruction achieve the largest increase in FEV1 during exercise (2). NO has been designated one of the possible candidates to exert these initial bronchodilator properties by inducing smooth muscle relaxation during exercise itself, thereby functionally opposing other mediators, such as histamine and leukotrienes, that contribute to the subsequent airway narrowing during and after exercise in asthma (17, 27).
Hence, endogenous production of NO during exercise may prevent worsening of exercise-induced bronchoconstriction (EIB) in asthma. On the other hand, endogenous NO might also contribute to EIB by enhancing bronchial hyperreactivity and vascular leakage during and after exercise (18, 48).

Various studies on the modulation of endogenous NO synthesis have revealed that NO is involved in the maintenance of bronchial tone. First, oral administration of L-arginine, the NOS substrate, has been shown to reduce airway reactivity to inhaled histamine (slope of the dose-response curve) in patients with mild asthma (15). Second, it has recently been demonstrated that inhibition of endogenous NO synthesis by nitro-L-arginine methyl ester (L-NAME) increased airway hyperresponsiveness (AHR, i.e., leftward shift of the dose-response curve) to histamine and AMP in asthmatic patients (44), suggesting protective effects against bronchoconstriction by NO within the airways. Similarly, inhalation of $\text{N}^\text{G}$-monomethyl-L-arginine (L-NMMA), another NOS inhibitor, increased AHR to bradykinin in mildly asthmatic patients (37), but not in patients with more severe asthma (36), thereby indicating a putative relationship between disease severity and a deficiency of bronchoprotective NO.

On the basis of these observations, it is unclear whether endogenous NO may act as a protective or a stimulatory factor in the airway response to exercise. Therefore, we examined, first, the role of endogenous NO in EIB by using inhaled L-NMMA as a pretreatment to exercise challenge in patients with asthma and in healthy controls. Second, we used inhaled L-arginine to examine whether a putative NO deficiency due to substrate limitation may contribute to EIB in asthmatic patients.

**METHODS**

**Subjects**

**Healthy controls.** Twelve nonsmoking, nonatopic, healthy subjects (age 19–37 yr) were asked to volunteer for the study (Table 1). Their baseline FEV$_1$ was $\geq$80% of predicted value, and none of the subjects demonstrated AHR to histamine [provocative concentration causing a 20% fall in FEV$_1$ (PC$_{20}$) $>16$ mg/ml]. Their nonatopic status was confirmed by a negative skin-prick test to 16 common airborne allergens (Vivodiagnost, ALK, Benelux).

**Asthmatic patients.** Twelve nonsmoking, atopic subjects with mild-to-moderate stable asthma (age 20–26 yr) participated in the study (Table 1). Their symptoms were controlled by inhaled short-acting $\beta_2$-agonists on demand only. None had used inhaled or oral corticosteroids within 3 mo before the study. All were hyperresponsive to histamine (PC$_{20}$ = 0.09–3.18 mg/ml), and their baseline FEV$_1$ was $\geq$70% of predicted (range 75–102% of predicted). Atopy was confirmed by a positive skin-prick test to $\geq$1 of 16 common airborne allergens (wheal $\geq$3 mm). All patients reported symptoms of EIB, which was confirmed by a fall in FEV$_1$ exceeding 10% from the baseline value after a 6-min exercise test at screening.

None of the patients had a history of upper respiratory tract infection or relevant allergen exposure during 2 wk before start of the study. Before testing, the patients were asked to refrain from inhaled short-acting bronchodilators for $\geq$8 h and from caffeine-containing beverages for $\geq$4 h. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center, and all patients gave informed consent.

**Study Design**

On 2 days before the study, the inclusion criteria were examined for each subject. The study had a double-blind, placebo-controlled, crossover design and was performed on 2 or 3 days separated by 48-h intervals. Standardized exercise challenge was started 15 min after randomized inhalation of L-NMMA or placebo treatment in healthy controls. Similarly, the asthmatic patients were treated with inhaled L-NMMA, L-arginine, or placebo on 3 randomized days. Additionally, FEV$_1$ was measured before and 10 min after inhalation of either treatment and subsequently every 4 min starting from 2 until 30 min after exercise. Additionally, to examine the effect of each treatment on endogenous NO synthesis, levels of exhaled NO were measured before and 5 min after inhalation of either treatment and every 4 min starting from 4 until 32 min after cessation of the exercise challenge.

**Pretreatment**

Freshly prepared L-NMMA (10 mg dissolved in 2 ml of $\text{H}_2\text{O}$ with addition of 1 ml of isotonic saline to give a total volume of 3 ml; Clinalfa, Häufelfingen, Switzerland) (14), L-arginine (375 mg in 3 ml $\text{H}_2\text{O}$; Clinalfa), or placebo (isotonic saline)...

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**Table 1. Subject characteristics**

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FEV$_1$, forced expiratory volume in 1 s; PC$_{20}$, provocative concentration of histamine causing a 20% fall in FEV$_1$; EIB, exercise-induced bronchoconstriction measured as maximal percent decline in FEV$_1$ from baseline after exercise challenge. Atopic status is measured as number of positive reactions (wheal $\geq$3 mm) to a skin-prick test to 16 common airborne allergens.
Exercise Challenge

Exercise challenge was performed according to a previously validated protocol (11, 42) using a bicycle ergometer. The work intensity was selected for each subject to achieve a minute ventilation of 40–50% of his or her predicted maximal voluntary ventilation (35 × FEV₁, predicted) during 6 min. Compressed dry air (20°C, 6–7% relative humidity) was administered through an air-supply bag connected to a Hans Rudolph three-way valve. The subjects wore a facemask covering the nose and mouth, while the nose was clipped to Rudolph three-way valve. The subjects wore a noseclip during inhalation.

Airway responses were measured by FEV₁, which was recorded on a dry rolling-seal spirometer (Spiroflow, Morgan/Gillingham). Three measurements of FEV₁ were performed before and immediately after treatment to calculate baseline values. The mean value after treatment was used as the preexercise baseline value in the analysis of the airway response to exercise. Single measurements of FEV₁ were performed every 4 min from 2 to 30 min after cessation of the exercise challenge.

Exhaled NO

Exhaled NO measurements were performed using a fast-response (response time 200 ms) chemiluminescence analyzer (model NOA 270B, Sievers, Boulder, CO) according to recent guidelines (40). The subjects were asked to perform a tachograph (Lilly principle, Erich Jaeger, Würzburg, Germany). Plateau levels of NO were determined and expressed as parts per billion (ppb). Measurements were discarded when the expiratory flow varied by >10% from target flow (100 ml/s). Before and 5 min after treatment, three successive recordings were made at 1-min intervals, and the mean was used in the analysis. Single exhaled NO measurements were carried out every 4 min up to 32 min after cessation of the exercise challenge, and changes were expressed as percent fall in exhaled NO from the posttreatment value.

Analysis

The bronchoconstrictor response to exercise was expressed as the maximal percent fall in FEV₁ from baseline value (asthmatic group only) and as the area under the curve over the 30-min postchallenge period (AUC). To stabilize variability (1), logarithmic transformation was applied for AUC. In the healthy control group, the value 150 was added to AUC before transformation to correct for negative areas (lowest area was −110.8). Student’s paired t-test was applied to test for differences in FEV₁, maximal percent fall (asthmatic group only), and AUC between each treatment and to examine baseline values for FEV₁ and exhaled NO before and after each treatment. Furthermore, multivariate ANOVA (MANOVA) was applied to explore the effect of treatment on FEV₁ and levels of exhaled NO after exercise in time. Subsequently, Student’s paired t-test was used to examine individual time points. P < 0.05 was considered statistically significant.

RESULTS

Healthy Controls

In the normal subjects, baseline FEV₁ was not different between both study days [99.4 ± 3.7 and 99.8 ± 3.5% of predicted (SE) with placebo and L-NMMA, respectively, P = 0.7] and was not significantly affected by either treatment (P > 0.3). There was also no difference in posttreatment FEV₁ between study days [98.6 ± 3.9 and 99.7 ± 3.7% of predicted with placebo and L-NMMA, respectively, P = 0.4]. Baseline exhaled NO levels were similar on both study days: 6.7 ± 0.7 and 6.7 ± 1.3 (SE) ppb with placebo and L-NMMA, respectively (P = 0.99). Inhalation of placebo or L-NMMA did not result in a significant change in levels of exhaled NO in healthy subjects: 7.1 ± 0.9 and 6.4 ± 1.3 ppb after placebo and L-NMMA, respectively (P > 0.4; Fig. 1A).

There was no significant difference in minute ventilations during exercise challenge between study days: 58.6 ± 4.4 and 58.8 ± 4.1 (SE) l/min with placebo and L-NMMA, respectively (P = 0.7). Mean time-response curves of FEV₁ to exercise after placebo and L-NMMA treatment are shown in Fig. 1B. Exercise induced a slight, but significant, increase in FEV₁ over time following placebo treatment (P = 0.015, MANOVA), whereas this could not be observed after L-NMMA (P = 0.15, MANOVA). However, there was no significant difference in exercise-induced change in FEV₁ between treatments over time (P = 0.7, MANOVA). Similarly, there was no difference in AUC between placebo and L-NMMA: 28.6 ± 17.0 and 1.3 ± 20.4%·h (SE), respectively (P = 0.18).

Asthmatic Patients

In the asthmatic patients, baseline FEV₁ was not different between the 3 study days: 91.8 ± 2.3, 88.5 ± 2.8, and 89.6 ± 2.4% of predicted with placebo, L-NMMA, and L-arginine, respectively (P = 0.06). Additionally, baseline FEV₁ was not affected by either treatment (P > 0.08), and posttreatment FEV₁ was also not different between study days: 90.4 ± 2.2, 88.9 ± 2.7, and 88.9 ± 2.4% of predicted with placebo, L-NMMA, and L-arginine, respectively (P = 0.6).

There was no significant difference between the 3 days in exhaled NO levels at baseline: 33.4 ± 7.8, 31.4 ± 8.3, and 32.9 ± 7.6 ppb with placebo, L-NMMA, and L-arginine, respectively (P = 0.76). However, a significant reduction in exhaled NO was observed 5 min after inhalation of L-NMMA (26.3 ± 7.2 ppb, P = 0.009) compared to placebo (15.4 ± 4.7 ppb, P = 0.012).
ROLE OF ENDOGENOUS NO IN RESPONSE TO EXERCISE

Exhaled NO in Response to Exercise Challenge

Exercise induced a markedly different response in exhaled NO levels over time between healthy subjects and asthmatic patients \((P = 0.02, \text{MANOVA}; \text{Fig. 3})\). In the asthmatic group, there was a significant decrease in exhaled NO levels immediately after exercise challenge, whereupon levels returned to baseline values \((P = 0.17, \text{MANOVA})\). Remarkably, however, a similar reduction in exhaled NO was found shortly after exercise in the healthy controls, followed by a significant increase at later time points \((P < 0.0001, \text{MANOVA})\).

DISCUSSION

The present results demonstrate that inhibition of endogenous NO production by inhaled L-NMMA does not significantly affect levels of exhaled NO in healthy controls, whereas it reduces those levels in patients with asthma. Likewise, inhalation of the NOS substrate L-arginine results in increased levels of exhaled NO in asthma. No effect of either treatment (i.e., L-NMMA and placebo) could be found on the airway response to exercise in healthy controls. However, even though the airway response to exercise after treatment with L-NMMA or L-arginine was not different from placebo, there was a tendency toward a slightly increased bronchoconstrictor response to exercise after treatment with inhaled L-arginine compared with L-NMMA in patients with asthma. These data, therefore, indicate that NO does not play a role in the airway response to exercise in healthy subjects but may be involved in mediating EIB in asthma. We speculate that endogenous NO primarily contributes to vasodilation, as opposed to smooth muscle relaxation, within the airway wall during exercise in asthma.

This is the first study examining the role of NO in the airway response to exercise in healthy subjects and asthmatic patients. Previous reports have considered only the effect of exercise on levels of exhaled NO in healthy controls, demonstrating an increased release of NO during and shortly after exercise \((6, 9, 20, 28, 33)\); others have suggested that this increased release of NO is merely a function of high flow rates during exercise \((41)\). This seems to be related to the increased ventilation, rather than the increased blood flow through the pulmonary circulation during exercise \((34)\). Some studies have provided circumstantial evidence for an inhibitory role of NO in the bronchoconstrictor response to exercise \((45, 46)\). Therminarias and colleagues \((46)\) demonstrated a reduced endogenous NO production concomitant with an induction of airway obstruction during exercise in healthy subjects breathing cold air. Additionally, Terada and colleagues \((45)\) showed increased levels of expired NO after exercise challenge in asthmatic patients without exercise-induced airway narrowing, whereas NO levels were reduced in asthmatic patients who developed airway obstruction after exercise. Remarkably, however, our present findings argue against such bronchoprotective involvement of NO in the airway response to exercise in healthy subjects and asthmatic patients. Hence, it

![Diagram](Image)

Fig. 1. A: individual levels of exhaled nitric oxide (NO) with corresponding mean (horizontal bars) in parts per billion (ppb) before (pre) and 5 min after (post) inhalation of placebo or N-monomethyl-L-arginine (L-NMMA, 10 mg) in 12 healthy controls. B: airway response to exercise challenge after treatment with inhaled placebo (○) or L-NMMA (●). Values are means ± SE expressed as percent change in forced expiratory volume in 1 s (FEV\(_1\)) from preexercise baseline value \((B)\) in 12 healthy volunteers.

0.009), whereas inhalation of L-arginine resulted in a rapid and significant increase in levels of exhaled NO \((39.7 ± 9.3, P = 0.004)\). No such change could be observed after placebo treatment \((32.8 ± 7.4 \text{ ppb}, P = 0.5; \text{Fig. 2A})\).

Minute ventilation during exercise challenge was not significantly different between study days: \(55.4 ± 3.1, 56.5 ± 3.3, \text{and} 56.4 ± 3.2 \text{ (SE) l/min with placebo, L-arginine, and L-NMMA, respectively (} P = 0.5, \text{MANOVA)}\). The airway responses to exercise after L-NMMA or L-arginine treatment were not significantly different from those with placebo, when analyzed as maximal percent fall in FEV\(_1\) \((22.2 ± 3.1, 18.9 ± 3.1, \text{and} 22.6 ± 3.3\% \text{ fall in FEV\(_1\) (SE) with placebo, L-NMMA, and L-arginine, respectively,} P > 0.3)\) or as AUC between L-NMMA or L-arginine treatment compared with placebo \([\text{geometric mean ± SE:} -204.3 ± 1.5 \text{ and} -186.9 ± 1.4\% \cdot \text{h with placebo and L-NMMA, respectively (} P = 0.7), \text{or} -318.1 ± 1.2\% \cdot \text{h with L-arginine (} P = 0.2)]\). However, there was a borderline significant difference in AUC between L-NMMA and L-arginine treatment \((P = 0.052; \text{Fig. 2B})\).
can be postulated that vascular effects of NO may have predominated over the smooth muscle relaxant effects during and after exercise.

In the present study, we have examined the role of NO on the airway response to exercise by using inhaled L-NMMA and/or L-arginine as a pretreatment in healthy subjects and asthmatic patients. First, it seems unlikely that the present findings can be explained by a lack of effect of treatment on endogenous NO synthesis. As previously demonstrated, the dose of L-NMMA (10 mg) was sufficient to reduce levels of exhaled NO by \( \frac{60}{6} \% \) within 30 min after inhalation in a group of 14 asthmatic patients meeting the same inclusion criteria (14). Furthermore, in a small dose-finding study, we determined the dose of L-arginine leading to a maximal increase in exhaled NO levels, while not affecting FEV\(_1\) by \(<5\%\). Yet, it seems contradictory that in the present study L-NMMA and L-arginine inhalation had only limited effects on exhaled NO levels as measured at 5 min posttreatment. However, the design of the present study was optimized for having the maximal modulation of endogenous NO levels by either treatment at the time of the exercise challenge and the subsequent recovery phase. Furthermore, the lack of effect by NO synthesis modulation on exhaled NO in the healthy subjects may be explained by the already low baseline levels of exhaled NO in this group. The borderline significance of the difference in airway responses to exercise between L-NMMA and L-arginine pretreatment may be the result of lack of statistical power, which was 33\% to detect such significant difference. The study should be repeated with 35 subjects to detect such difference between L-NMMA and L-arginine with a power of 80\% and a significance level of 5\%. Finally, it is unlikely that the present

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**Fig. 2.** A: levels of exhaled NO with corresponding mean (horizontal bars) before and 5 min after inhalation of placebo, L-NMMA (10 mg), or L-arginine (375 mg) in 12 patients with asthma. B: bronchoconstrictor response to exercise challenge after treatment with inhaled placebo (○), L-NMMA (●), or L-arginine (▲). Values are means ± SE expressed as percent change in FEV\(_1\) from preexercise baseline value in 12 patients with mild-to-moderate asthma.

**Fig. 3.** Percent change in levels of exhaled NO from preexercise baseline value after exercise challenge in healthy controls and patients with asthma. Values are means ± SE. *P < 0.05 compared with preexercise baseline value in healthy controls. *P < 0.05 compared with preexercise baseline value in asthmatic patients.
results can be explained by measurement errors, since we used validated methodology for exercise testing (11, 42) and exhaled NO measurement (40). Moreover, to exclude possible differences in NOS activity based on airway inflammation and atopy, we selected a homogeneous group of nonsmoking, nonatopic, healthy subjects and a group of nonsmoking, atopic patients with mild-to-moderate asthma not using any steroid treatment, while none had a history of respiratory viral infection.

How can the present results be explained? The level of ventilation during exercise seems to be the major determinant for the severity of EIB in asthma. Transient hyperosmolarity or cooling of the airway mucosa due to water loss is thought to be the stimulus that induces airway smooth muscle contraction, microvascular hyperemia, and/or edema (2). Indeed, it has been demonstrated that a hyperosmolar stimulus can result in increased vascular permeability (47), while a reduction in airway temperature can lead to bronchial hyperemia (29). Because airway inflammation, such as in asthma, has been associated with increased airway wall vascularity (26, 32) and enhanced airway mucosal blood flow (25), hyperemia and vascular leakage may be enhanced in asthma, leading to an increased bronchoconstriction, in addition to that caused by release of leukotrienes and histamine, during and particularly after exercise (18).

It has been demonstrated that exercise results in increased concentrations of circulating NO (31), most probably caused by the increased blood flow, which is known to be an important trigger for the release of NO by vascular endothelial cells (39), although this could not be confirmed by others (35, 41). Additionally, endogenous NO has been shown to be an important factor in the modulation of peripheral vascular tone (48) and in the prevention of hypoxic pulmonary, and probably also bronchial, vasoconstriction (4, 43). Consequently, it seems likely that an enhanced production of endogenous NO is involved in the reduction of pulmonary vascular resistance during exercise. Several studies have examined the possible pulmonary hemodynamic function of NO during exercise. In sheep, intravenous administration of an NOS inhibitor revealed vasodilator properties of NO at rest, but this activity of NO was not enhanced during exercise (24). The effects of NOS inhibition could be reversed by the NOS substrate l-arginine, but l-arginine had no independent vasodilator effect on the pulmonary circulation during exercise in sheep. Similar functions of NO have recently been observed during exercise in healthy men (7). Furthermore, no effects on pulmonary hemodynamics could be demonstrated after inhalation of NO in animals and in humans (8, 24). It is not unlikely that inhalation of l-arginine, in the present study, resulted in a further increase of airway mucosal blood flow (25, 26) and an enhanced bronchial vascular permeability and hyperemia, whereas opposite effects may have occurred after inhalation of l-NMMA in patients with asthma. This might explain the slight, but not significantly, enhanced EIB by l-arginine as opposed to l-NMMA as observed in asthma.

The initial reduction in exhaled NO after exercise challenge in both groups corresponds with previous findings in healthy controls (9, 46). An interesting observation was the significant increase in exhaled NO levels >20 min after cessation of exercise challenge in healthy subjects, whereas such an increase could not be observed in patients with asthma. Similar data have been described by Terada and colleagues (45) showing an increase in expired NO levels after exercise challenge in healthy subjects, as opposed to a reduction in asthmatic patients. Such an increase in normal subjects might be a delayed consequence of the exercise-induced increase in levels of circulating plasma NO (31) diffusing into the alveolar space. On the other hand, in analogy with the effects of blood flow on endothelial NO production (24), it can be speculated that the postexercise increase in exhaled NO might be the result of an increased NO production due to shear stress of the bronchial wall, as is likely to occur during exercise. The absence of an exercise-induced increase in exhaled NO in asthma is intriguing and might be explained by the acute airway obstruction after exercise. In a previous study in our laboratory, we demonstrated that acute reduction in airway caliber is associated with a fall in exhaled NO levels (13). However, further studies are warranted to elucidate the background of this phenomenon during exercise.

In conclusion, we have observed that NO synthesis inhibition slightly, but not significantly, attenuates EIB compared with supplementation of NOS substrate in patients with asthma. Modulation of endogenous NO synthesis did not affect the airway response to exercise in healthy subjects. These results suggest that endogenous NO does not inhibit the bronchoconstrictor response to exercise in asthma.

REFERENCES


