

Morning-to-evening variation in exercise-induced bronchospasm

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Background: Exercise is one of the most common triggers of asthmatic symptoms. Many factors, including hyperventilation, determine the prevalence and severity of exercise-induced bronchospasm (EIB). However, the influence of time of day has not been adequately described.

Objective: We sought to compare morning and evening EIB and minute ventilation during exercise (VE).

Methods: Twenty-two patients with stable asthma and 12 control subjects underwent exercise challenge at 7 AM and 6 PM. The time of the first challenge was randomly assigned; the second challenge was performed within 1 week of the first. The primary outcomes were EIB intensity (maximum fall in FEV₁) and VE. **Results:** The asthma group exhibited lower EIB values in the morning: 14.8% ± 3.7% at 7 AM vs 21.4% ± 4.2% at 6 PM ($P = .004$)—ie, 0.37 ± 0.09 L vs 0.53 ± 0.10 L, respectively ($P = .002$). VE was higher at 7 AM (55.4 ± 4.7 L/min) than at 6 PM (52.4 ± 4.3 L/min; $P = .03$). Baseline FEV₁ increased from 2.33 ± 0.13 L (morning) to 2.49 ± 0.15 L (evening; $P = .04$), and a significant correlation between baseline FEV₁ and EIB was found in the evening ($r = +0.5$; $P = .049$) but not in the morning. Post-exercise FEV₁ was similar at 7 AM (1.96 ± 0.13 L) and 6 PM (1.97 ± 0.14 L). For the control group, no changes were detected in FEV₁ fall or VE.

Conclusion: Baseline airway caliber contributes to the mechanisms of the morning-to-evening EIB enhancement. (*J Allergy Clin Immunol* 2002;110:236-40.)

Key words: Asthma, exercise-induced asthma, bronchial hyperreactivity, airway obstruction, circadian rhythm, pulmonary ventilation

Exercise is one of the most common triggers of acute asthmatic symptoms. The term *exercise-induced bronchospasm* (EIB) refers to the transient narrowing of the airways that follows vigorous exercise. The mechanism whereby EIB occurs is thought to relate to the consequences of heating and humidifying large volumes of air during exercise.^{1,2} The exercise ventilation and the heat content of the inspired air (ie, the product of temperature and water content) determine the airway response.

Abbreviations used

EIB: Exercise-induced bronchospasm
HR: Heart rate
VE: Minute ventilation during exercise

Accordingly, many factors help to determine the prevalence and severity of EIB: type of exercise, environmental conditions, asthma severity, and pre-exercise treatment.³⁻⁵ However, very few studies have tested the influence of time of day on intensity of EIB.^{6,7}

Nocturnal worsening of asthma has become a recognized and important aspect of the disease and must be considered in the management of the disease process. For the diurnally active asthmatic patient, a circadian pattern in lung function occurs, the lung function peak occurring at approximately 4 PM and the nadir at approximately 4 AM.⁸ A combination of factors sets in motion the asthmatic response at night. It is important to understand these responses, because treatment using chronotherapeutic principles can not only greatly improve the nocturnal aspect of asthma but also improve daytime symptoms and function.⁹⁻¹¹

The purpose of the present study was to make a comparison between the EIB in the morning and the EIB in the evening. We also evaluated the exercise ventilation at 7 AM and 6 PM to verify that EIB differences from morning to evening could be due to changes in the degree of ventilation.

METHODS

Twenty-two patients with asthma were enrolled in this prospective trial. Asthma was defined according to medical history, physical examination findings, and a methacholine PC₂₀ of <8 mg/mL and/or an FEV₁ improvement by inhaled β_2 -agonist (200 μ g albuterol) of >15%.¹² Twelve normal volunteers who were nonatopic and had FEV₁ values of at least 90% of predicted formed a control group. Exclusion criteria included a history of cigarette smoking, any other pulmonary or nonpulmonary disease, pregnancy, and documented or suspected respiratory tract infection or the use of systemic corticosteroids within 4 weeks before study entry. Informed consent was obtained for this Institutional Review Board–approved protocol.

Protocol

The study consisted of 2 exercise challenge tests (morning and evening), 36 hours to 7 days apart. Subjects were randomly assigned to start with either the 7 AM test or the 6 PM test; equal numbers of subjects started in the morning and in the evening. Asth-

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TABLE I. Subjects' characteristics

	Asthma group	Control group
No. of subjects	22	12
Sex (male/female)	12/10	6/6
Age (y)	31 ± 2	22 ± 2
FEV ₁ (L)	2.3 ± 0.1	3.7 ± 0.2
FEV ₁ (%)	65.9 ± 3.1	95.9 ± 3.1
FEV ₁ bronchodilator response (%)	14.4 ± 2.4	—
Medication in use (% of patients)		
β-agonist (short-acting)	100	—
β-agonist (long-acting)	23	—
Inhaled corticosteroids	64	—
Theophylline	14	—
Ipratropium bromide	32	—

ma medication was not modified between the 2 study visits. To ensure that a maximal exercise-induced response would occur, each subject withheld all medication for 12 hours before each session. Long-acting β₂-agonist and sustained-release oral theophylline were withheld for at least 24 hours. Moreover, the time interval between the last dose of bronchodilator and the exercise test was established to be the same before both tests.

Exercise test

Exercise challenge tests were performed on a treadmill through use of a 6-minute challenge protocol. With the aid of air conditioning apparatus, the exercise laboratory temperature and relative humidity were kept at 20° to 22°C and 50% to 55%, respectively. After 1 minute of light exercise on the inclined (10°) treadmill, the speed was quickly increased to achieve a heart rate (HR) corresponding to 80% of the maximum predicted HR (220 – age); this speed was then maintained for 6 minutes. This target workload was selected to produce an intense exercise, with high ventilatory rates and great heat and water loss via the bronchial mucosa. Rates of minute ventilation during exercise (VE) were measured by means of a pneumotachograph (Brass Fleisch-type). At every minute during exercise, values for VE were calculated from 15-second averages of the breath-by-breath data. Patients were asked about the intensity of dyspnea at every minute during exercise and immediately before every FEV₁ measurement (modified Borg scale).^{13,14} Oxyhemoglobin saturation was monitored throughout the study by means of an oxymeter (DX7100, Dixtal Biomedica Ind, São Paulo, Brazil), and HR was measured with a Polar HR monitor (Polar Beat, Polar Electro Inc, Kempele, Finland). Standard measurements of spirometry were obtained before, immediately after, and 5, 10, 15, 20, 30, and 45 minutes after exercise. The tests were done with a Koko spirometer and software (PDS Instrumentation, Inc, Louisville, Colo). The maximum percentage change from baseline was calculated as 100 × the decrease in FEV₁/baseline FEV₁.¹⁵ The FEV₁ was chosen for the recording of exercise-induced bronchial responses because FEV₁ reductions are more reproducible.¹⁶

Statistical analysis

Regarding primary outcomes, EIB intensity, and VE, data were analyzed through use of a 2-tailed Student paired *t* test for morning-to-evening comparisons. For EIB, both the maximum percentage change from baseline (%) and the maximum change from baseline (in liters) were used to compare results. Relationships between degree of EIB and VE or FEV₁ for both morning and evening measurements were calculated through use of a Pearson correlation coefficient.^{17,18} Comparisons between groups were performed with a Student unpaired *t* test. Data were expressed as means ± SEMs. *P* values less than .05 were considered significant.

TABLE II. Exercise-induced bronchospasm: morning-to-evening variation

	Morning	Evening
Control group (n = 12)		
Baseline FEV ₁	3.74 ± 0.22	3.70 ± 0.25
Post-exercise FEV ₁	3.64 ± 0.22	3.58 ± 0.23
FEV ₁ fall (L)	0.10 ± 0.09	0.13 ± 0.09
VE (L/min)	60.1 ± 7.6	63.3 ± 7.8
Asthma group (n = 22)		
Baseline FEV ₁	2.33 ± 0.13	2.49 ± 0.15*
Post-exercise FEV ₁	1.96 ± 0.13	1.97 ± 0.14
FEV ₁ fall (L)	0.37 ± 0.09	0.53 ± 0.10*
VE (L/min)	55.4 ± 4.7	52.4 ± 4.3*

**P* < .05 in comparison with morning values.

RESULTS

Subject characteristics of the asthma and control groups are shown in Table I. The intensity of EIB was greater in the evening than in the morning according to both analyses of FEV₁ fall, percentage of baseline and absolute fall (in liters). The percentage of decrease in FEV₁ was 14.8% ± 3.7% in the morning and 21.4% ± 4.2% in the evening (*P* = .004); these corresponded to a fall of 0.37 ± 0.09 L in the morning and a fall of 0.53 ± 0.10 L in the evening (*P* = .002; Table II). When we defined an FEV₁ fall of ≥10% as positive for EIB, 14 patients (64%) had EIB at either one or both time points. For this subset of patients, the EIB values were 23% ± 4.2% and 31.4% ± 4.9% (*P* = .01) in the morning and evening, respectively—ie, 0.54 ± 0.12 L and 0.77 ± 0.12 L (*P* = .004) in the morning and evening, respectively (Fig 1). Fig 2 shows the time course of FEV₁ fall at both time points.

The VE value was higher at 7 AM (55.4 ± 4.7 L/min) than at 6 PM (52.4 ± 4.3 L/min; *P* = .03) in the asthma group (Table II). No significant correlation between EIB and VE was found at any time. Baseline (pre-exercise) FEV₁ was higher in the evening than in the morning (2.49 ± 0.15 L; 2.33 ± 0.13 L; *P* = .04). Post-exercise FEV₁ values were not significantly different (morning, 1.96 ± 0.13 L; evening, 1.97 ± 0.14 L; Table II). A significant positive correlation was found between baseline FEV₁ value and EIB magnitude in the evening (*r* = +0.5; *P* = .049); however, in the morning, baseline FEV₁ was not significantly correlated with EIB severity (*r* = +0.3; *P* = .13).

For the control group, neither did EIB nor VE exhibit significant morning-to-evening change (Table II).

Dyspnea was analyzed by comparing morning and evening highest scores obtained during exercise. A similar comparison was made for the post-exercise dyspnea scores. The maximum scores during exercise were 2.9 ± 0.3 and 2.1 ± 0.5 at 7 AM and 6 PM, respectively. After exercise, morning dyspnea was 2.4 ± 0.3 and evening dyspnea was 2.9 ± 0.5. The highest dyspnea scores for the control group were 2.2 ± 0.3 (morning) and 1.7 ± 0.3 (evening) during exercise and 1.1 ± 0.3 (morning) and 1.2 ± 0.3 (evening) after exercise. Morning-to-evening differences were not statistically significant. However, between-groups comparisons demonstrated

Asthma, rhinitis,
other respiratory
diseases

Exercise-Induced Bronchospasm

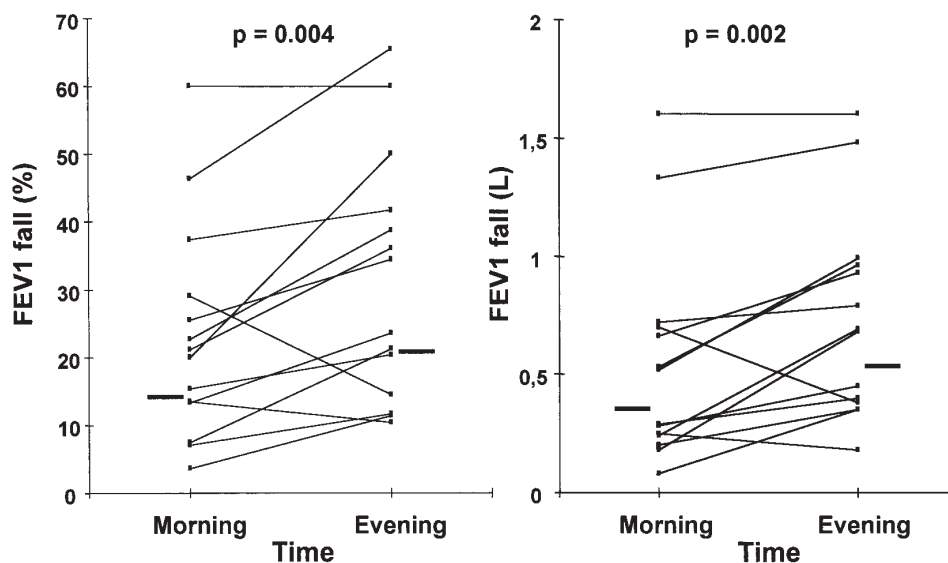


FIG 1. Evening EIB intensity was greater for both depicted analyses, maximum percentage fall in FEV_1 (%) and maximum fall in FEV_1 (in liters). Each of these asthmatic patients presented a fall of at least 10%.

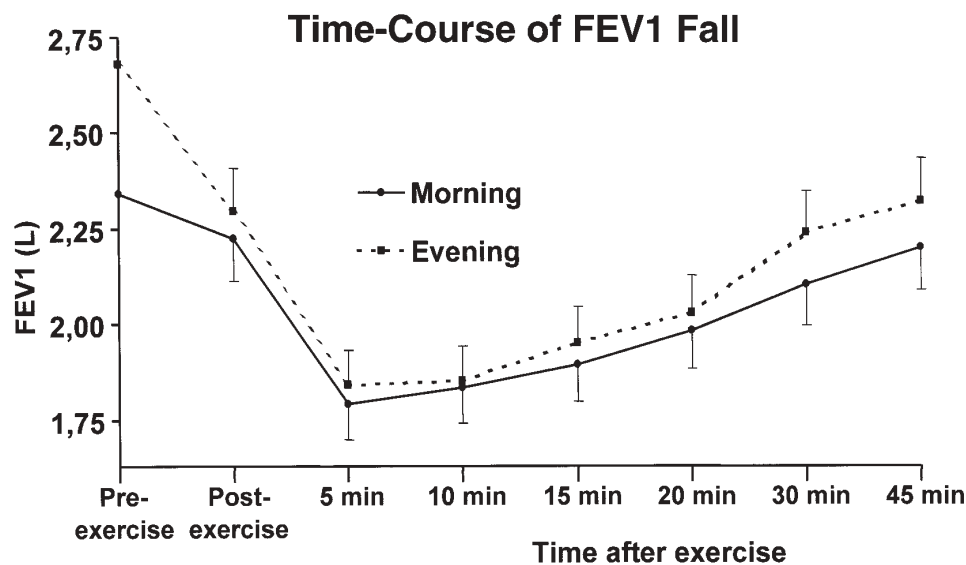


FIG 2. FEV_1 (mean $\pm$ SEM) after exercise at 7 AM (Morning) and at 6 PM (Evening). The baseline FEV_1 and FEV_1 fall were greater in the evening than in the morning ($P < .05$). Each of these asthmatic patients presented a fall of at least 10% ($n = 14$).

that in the post-exercise period, asthmatic patients had higher dyspnea scores at 7 AM ($P = .012$) and at 6 PM ($P = .035$). During exercise, asthma and control groups' scores were comparable.

DISCUSSION

We found that patients with moderate asthma had more intense EIB in the evening than in the morning. On

the other hand, ventilation during exercise was greater in the morning, with no correlation between VE and EIB. A morning-to-evening variation in baseline FEV_1 was also found, with higher values at 6 PM than at 7 AM, as would be expected. Normal volunteers did not show any significant difference related to these parameters. The evaluation of dyspnea according to the Borg scale during and after exercise did not show morning-to-evening changes, though the asthma group had higher dyspnea scores than

the control group in the post-exercise evaluation at both the 7 AM and 6 PM time points.

The degree of ventilation during exercise does not seem to be an explanation for the EIB increase from morning to evening, because VE decreased when EIB increased (with no statistical relationship). It is probable that the higher ventilation in the morning was a consequence of the lower FEV₁ and that small shifts in VE do not induce significant changes in EIB. The baseline FEV₁ is a possible causal factor for the EIB variation. The highest FEV₁ in the evening might predispose to the biggest fall. This theory is supported by the following study findings: (1) a significant increase in pre-exercise FEV₁ values from 7 AM to 6 PM; (2) a positive correlation between pre-exercise FEV₁ and EIB at 6 PM but not at 7 AM; and (3) similarity of morning and evening post-exercise FEV₁ values, which could also indicate a limit for the FEV₁ fall.

In a study by Bundgaard and Andersen,⁷ baseline peak expiratory flow rates were rendered similar by histamine inhalation before exercise challenges at 4 time points in the same day. The authors concluded that when the baseline values are the same, there is no diurnal variation in the response to exercise. It is worth mentioning that EIB refractoriness¹⁹ was not contemplated in the design of their study; in addition, measurement of peak expiratory flow rate instead of FEV₁ in a small population at several time points might have obscured the statistical significance of the observed morning-to-afternoon increase in EIB.

One could also argue that increased EIB in the evening is a consequence of an increase in bronchial hyperresponsiveness. Circadian variation in nonspecific bronchial responsiveness has been described by several authors.²⁰⁻²³ Most of these studies evaluated circadian changes in bronchial response to pharmacologic agents and concluded that nonspecific airway responsiveness is enhanced at night, especially in patients who experience a significant nocturnal increase in airway obstruction. In these studies, the maximal responsiveness to histamine, methacholine, or acetylcholine was seen during the night, at approximately 4:00 AM.

The temporal pattern in bronchial response to the hyperventilation of cold dry air is different. Like us, Sly and Landau²⁴ found that children are most sensitive to hyperventilation of cold dry air in the afternoon, at 4 PM. In a recent review article on circadian variation in bronchial responsiveness, Jarjour²⁵ pointed out that different mechanisms might be responsible for the circadian changes in responsiveness to various "nonspecific" challenges. However, at the time he wrote his report, the author considered it difficult to speculate on the potential causes because of the limited data available, particularly with regard to responsiveness to exercise or cold air challenges.

In any case, the described phenomenon has clinical implications that are relevant, and these should be taken into account by doctors and health professionals dealing with exercise and asthma. The time of day that an exercise challenge is performed might interfere with the yield of the test. According to our data, the morning is not the best time to detect exercise-induced bronchial responses, though

additional data are still necessary for comparison of different time points with respect to the incidence of EIB in larger asthmatic populations. In addition, clinical trials based on EIB could also be designed to schedule tests in the evening or afternoon to achieve better signaling. The consideration here is that the better a drug works in protecting against EIB, the greater will be the subject's response and the easier it will be to show a statistically significant drug effect. Finally, a better understanding of the complex interaction between asthma and exercise could provide ways by which to improve the clinical management of asthma, especially in the case of patients with EIB.

In conclusion, EIB is more intense in the evening than in the morning; however, symptoms related to exercise are not greater in the evening. The variation in EIB is not related to the degree of ventilation during exercise, which is higher in the morning. The baseline airway caliber might play a role in the mechanism of the EIB morning-to-evening enhancement. Further studies should compare the EIB intensity from morning to evening in patients without significant lung function variation or should warrant similar baseline function by pre-exercise treatment with medication that undoubtedly has no effect on EIB to corroborate the baseline airway function importance of this phenomenon.

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