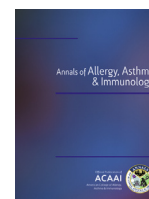




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Letter

Rethinking the prevalence of exercise-induced bronchoconstriction in patients with asthma

Exercise-induced bronchoconstriction (EIB) is reported in up to 90% of patients with asthma.^{1–3} However, the body of literature reporting these estimates is confounded by varying diagnostic methods, the use of different measures and modes of challenges, and a relative lack of population-based studies. Athlete⁴ and military⁵ cohorts dominate the epidemiologic data.

The current standard criterion for diagnosis of EIB is a 10% or greater decrease in forced expiratory volume in 1 second (FEV₁) after exercise challenge^{6,7}; however, thresholds of 15%^{3,7} and 20%⁸ have also been suggested for greater diagnostic stringency. This variation in methods and populations may conspire to inflate the prevalence of EIB compared with that found in an urban US population.

In a randomized, double-blind, placebo-controlled, crossover study (clinicaltrials.gov identifier NCT01070888), we investigated the efficacy of inhaled budesonide and formoterol to treat EIB compared with budesonide alone. Nonsmoking subjects, 12 to 50 years old, with mild-moderate to persistent asthma of 6 months or longer who were taking a stable dose of inhaled corticosteroids (ICSs) and who reported exercise-induced asthma symptoms (positive response to the question, “Do you currently experience asthma symptoms during exercise?”) were screened for enrollment. Subjects taking long-acting β -agonists or oral corticosteroids were excluded. Recruitment entailed advertising in local hospitals, universities, gyms, newspapers, and online classifieds/employment sites around metropolitan Boston.

At screening, subjects underwent a standardized step-exercise challenge while breathing cooled dry air.⁶ A minimum of 3 acceptable spirometry efforts were performed before and after challenge at 0, 5, 10, 15, 30, 45, and 60 minutes. Maximal percentage decrease in FEV₁ was the percentage change from the preexercise FEV₁ to the minimum postexercise FEV₁. A cutoff of a 15% decrease in FEV₁ was used for inclusion based on the higher diagnostic utility⁶ for EIB than the 10% clinically used. Poor enrollment secondary to insufficient number of subjects attaining a 15% decrease in FEV₁ prompted a change in study design to include a 2-week, controller-free run-in period before exercise challenge. Two weeks was chosen to minimize ICS effect on exercise without risking significant loss of asthma control. Thus, 2 distinct groups, one challenged on their prescribed low- to medium-dose ICS (group 1) and another not taking controller medications (group 2), ultimately characterized our population.

Drs Gaffin and Bouzaher are both first authors.

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Of the 46 subjects screened, 33 (72%) successfully completed the exercise challenge testing. Thirteen subjects were unable to complete the challenge because of physical discomfort ($n = 7$), abnormal electrocardiography results ($n = 2$), hypertension ($n = 1$), and poor spirometry technique ($n = 3$). The cohort consisted of young adults with a mean age of 26 years who had asthma for a mean of 12 years. Three-quarters of the cohort were female and half were white. The mean body mass index was 25.

As expected, the prevalence of exercise-induced asthma decreased with increasing thresholds of FEV₁; at 10%, 15%, and 20%, 10 of 33 subjects (30%), 6 of 33 subjects (18%), and 4 of 33 subjects (12%), respectively, met the criteria for a positive exercise challenge result.

Subjects who underwent an exercise challenge after a controller-free run-in period had a greater decrease in FEV₁ than those who were challenged while taking their current ICS (Kruskal-Wallis test, $P = .03$). Comparatively, a greater proportion of subjects not taking controller medications during the run-in period met the criteria for EIB for the study ($\geq 15\%$ decrease in FEV₁: group 2, 5/15; group 1, 1/18; Fisher exact test, $P = .07$) and the clinical criteria for EIB ($\geq 10\%$ decrease in FEV₁: group 2, 8/15; group 1, 2/18; Fisher exact test, $P = .02$; Figure 1). Thus, even after implementing a washout period for ICSs, only 33% of participants met the study criteria and only half met the clinical criteria for EIB.

Despite the literature reporting high rates of EIB in patients with asthma,^{1,3,5,9} rates of EIB found in this study and others^{10–13} that

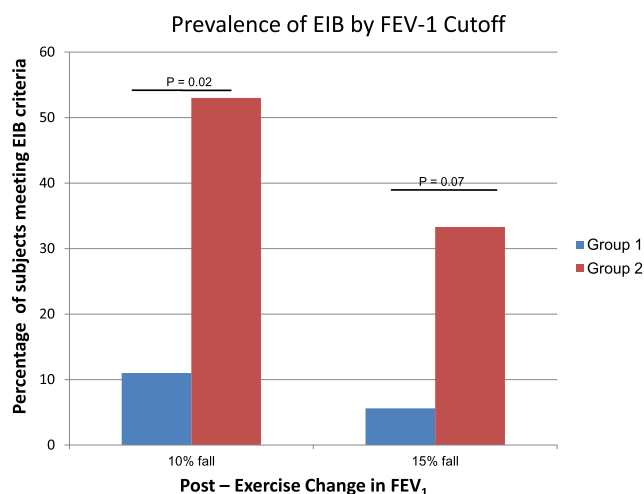


Figure 1. Exercise challenge on low- to medium-dose inhaled corticosteroids (group 1). Exercise challenge without controller medications (group 2).

enlisted rigorous EIB protocols in cohorts with symptoms of EIB have found much lower rates. Potential reasons for the discrepancy between these results may be variable measures of EIB, variable thresholds for determining a positive test result, and differences in populations tested. The type, duration, and intensity of the exercise procedure and the ambient conditions also may affect the results. Guidelines⁶ have been developed for EIB tests using spirometry to minimize these factors. Different thresholds for determining a positive test result have also been adopted. Clinical testing favors high sensitivity, and therefore a decrease of 10% in FEV₁ is considered diagnostic. However, in the research community optimizing specificity by increasing the threshold to 15% or 20% is more advantageous in differentiating the treatment effects of drugs. In this regard, the incidence of EIB may be underestimated because of the higher cutoffs. In contrast, clinical trials that enrich the screened population by only selecting patients with known airway hyper-reactivity¹³ and withdrawing all medications that may mitigate EIB^{11,12} should increase the likelihood of finding patients with true EIB. Lastly, differences in population demographics may contribute to some of the discrepancy. Compared with the historical literature, which largely focuses on elite athletes and military conscripts,⁵ our screened population was notably urban and typically overweight. Prior studies sampling the general asthma population also found lower prevalence of EIB (44%–60%^{10–13}) than typically referenced, which may support the theory that demographics play a role in EIB. In such populations, alternate diagnoses for exercise-induced dyspnea, such as deconditioning or obesity, are more likely to play a role than those enrolling athletes. Despite using standardized practices, our study found exceedingly low rates for EIB in patients with asthma endorsing exercise-induced symptoms, even when not taking controller medications.

Our primary study aim met with futility because of the relatively low prevalence of EIB in an urban sample of asthmatic patients, despite reporting symptoms of EIB. However, we were able to successfully demonstrate a significant improvement in identifying true EIB in this population after a washout of all controller medications. The limited prevalence of EIB in the general population of children and adults with asthma is important to consider in the design of clinical trials. Moreover, these data challenge the popular conception that EIB is highly prevalent in the general asthma population.

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