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Rethinking the Prevalence of Exercise Induced Bronchoconstriction in Patients with Asthma

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Exercise induced bronchoconstriction (EIB) is reported in up to 90 percent of patients with asthma¹⁻³. However, the body of literature leading to these estimates is confounded by varying diagnostic methodologies, employing different measures and modes of challenges, and relative lack of population-based studies. Athlete⁴ and military⁵ cohorts dominate the epidemiologic data.

Current standard criteria for diagnosis of EIB is 10% fall in FEV₁ post-exercise challenge^{6,7}. However, thresholds of 15%^{3,7} and 20%⁸ percent have also been suggested for greater diagnostic stringency. This variation in methods and populations may conspire to inflate the prevalence of EIB compared to that found in an urban US population.

In a randomized, double blind, placebo controlled, crossover study (ClinicalTrials.govIdentifier: NCT01070888) we investigated the efficacy of inhaled budesonide/formoterol to treat EIB compared to budesonide, alone. Non-smoking subjects, 12 to 50 years old, with mild-moderate to persistent asthma 6months, on a stable dose of inhaled corticosteroids (ICS), and who reported exercise induced asthma symptoms (positive response to: "Do you currently experience asthma symptoms during exercise?") were screened for enrollment. Subjects taking long acting beta agonist (LABA) or oral corticosteroids were excluded. Recruitment entailed advertising in local hospitals, universities, gyms, newspapers, and online classifieds/employment sites around metropolitan Boston.

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Author Contributions:

Dr. Gaffin contributed to the conception and design of the study, data generation, analysis and interpretation of the data, and preparation of the manuscript.

Ms. Bouzaher contributed to the design of the study, data generation, analysis and interpretation of the data, and preparation of the manuscript.

Dr. McCown contributed to the conception and design of the study, data generation, and critical revision of the manuscript.

Dr. Larabee Tuttle contributed to the conception and design of the study, data generation, and critical revision of the manuscript.

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At screening, subjects underwent a standardized step-exercise challenge while breathing cooled dry air⁶. A minimum of 3 acceptable spirometry efforts were performed pre- and post-challenge at 0, 5, 10, 15, 30, 45, and 60 minutes. Maximal percent decline in FEV₁ was the percentage change from the pre-exercise FEV₁ to the minimum post-exercise FEV₁. A cutoff of 15% decline 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% fall in FEV₁ prompted a change in study design to include a 2 week controller-free run-in period prior to exercise challenge. Two weeks was chosen to minimize ICS effect on exercise without risking significant loss of asthma control. Thus, two distinct groups, one challenged on their prescribed low–medium dose ICS (Group 1) and another off controller medications (Group 2), ultimately characterized our population.

Of the 46 subjects screened, 33 (71.7%) successfully completed the exercise challenge testing. Thirteen patients were unable to complete the challenge due to physical discomfort (7), abnormal ECG results (2), hypertension(1), and poor spirometry technique (3). The cohort consisted of young adults with an average age of 26 years old and had asthma an average of 12 years. Three quarters of the cohort was female and half were Caucasian. The mean body mass index (BMI) was 25.

As expected, the prevalence of EIA decreased with increasing thresholds of percent FEV₁ ; at 10%, 15%, and 20%, 10 out of 33 patients (30%), 6 out of 33 patients (18%), and 4 out of 33 patients (12%), respectively, met criteria for a positive exercise challenge.

Subjects who underwent an exercise challenge after a controller-free run-in demonstrated greater fall in FEV₁ than those who were challenged on their current inhaled corticosteroid (Kruskal–Wallis, $p = 0.03$). Comparatively, a greater proportion of subjects run-in off controller medications met criteria for EIB for the study ($\geq 15\%$ fall FEV₁, Group 2: 5/15 vs. Group 1: 1/18, Fisher exact $P = 0.07$) and clinical criteria for EIB ($\geq 10\%$ fall in FEV₁, Group 2: 8/15 vs. Group 1: 2/18, Fisher exact $P = 0.02$, see Figure). Thus, even after implementing a washout period of ICS medication, only 33% of participants met study criteria and only half met clinical criteria for EIB.

Despite literature suggesting high rates of EIB in patients with asthma^{1,3,5,9}, rates of EIB found in this study and others^{10–13} which 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 due to variable measures of EIB, variable thresholds for determining a positive test, 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 have also been adopted. Clinical testing favors high sensitivity and therefore a fall 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 treatment effects of drugs. In this regard the incidence of EIB may be underestimated due to the higher cut-offs. In contrast, clinical trials that enrich the screened population by only selecting subjects with known airway hyperreactivity¹³ and withdrawing all medications that may mitigate EIB^{11,12} should increase the likelihood of finding subjects with true EIB. Lastly, differences in population demographics may contribute to some of the discrepancy. In comparison to the historic literature which largely focuses on elite athletes and military conscripts⁵, the demographic included in 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 demographics playing a role. 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 subjects with asthma endorsing exercise induced symptoms even when off of controller medications.

Our primary study aim met with futility due to relatively low prevalence of EIB in an urban sample of asthmatic subjects, *despite reporting symptoms of EIB*. However, we were able to successfully demonstrate a significant improvement in better 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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Prevalence of EIB by FEV₁ Cutoff

Figure 1. Group 1, exercise challenge on low – medium dose inhaled corticosteroids. Group 2, exercise challenge off of controller medications.