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Reproducibility of the bronchoconstrictive response to eucapnic voluntary hyperpnoea

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ABSTRACT

Background: Eucapnic voluntary hyperpnoea (EVH) is considered an effective bronchoprovocation challenge for identifying exercise-induced bronchoconstriction (EIB). However, the reproducibility of the hyperpnoea-induced bronchoconstriction (HIB) response elicited by EVH remains unknown and was therefore the focus of this study.

Methods: Two cohorts of 16 physically active males (each cohort comprised 8 controls and 8 with physician diagnosis of asthma) participated in two studies of the short- and long-term reproducibility of the bronchoconstrictive response to an EVH test with dry air. EVH was performed on days 0, 7, 14, and 21 (short-term study), and 0, 35, and 70 (long-term study). HIB was diagnosed by a ≥10% fall in forced expiratory volume in 1 s (FEV_1) after EVH.

Results: On day 0 of the short-term study, FEV_1 fell by 2 ± 1% ($P < 0.05$) and 27 ± 18% ($P < 0.01$) from pre- to post-EVH in control and HIB-positive groups respectively. The post-EVH fall in FEV_1 did not differ across the short-term study test days. In the HIB-positive group, the day-to-day coefficient of variation, reproducibility, and smallest meaningful change for the fall in FEV_1 were 12%, 328 mL, and 164 mL, respectively. On day 0 of the long-term study, FEV_1 fell by 2 ± 2% and 25 ± 18% ($P < 0.01$) after EVH in control and HIB-positive groups respectively. The post-EVH fall in FEV_1 did not differ across the long-term study test days. In the HIB-positive group, the day-to-day coefficient of variation, reproducibility, and smallest meaningful change for the fall in FEV_1 were 10%, 196 mL, and 98 mL respectively.

Conclusion: The EVH test elicits a reproducible bronchoconstrictive response in physically active males with physician diagnosed asthma. These data thus support the clinical utility of the EVH test for EIB screening and monitoring.

1. Introduction

Asthma affects 5–10% of the population in developed countries [1] and is the most common chronic medical condition reported among Olympic athletes with a prevalence of around 8% [2]. At least 80% of individuals with clinically diagnosed asthma [3] and up to 50% of particular elite athlete populations [4] will also experience exercise-induced bronchoconstriction (EIB). EIB is characterised by transient airway narrowing during or after exercise and is ascribed to airway drying and subsequent changes in airway osmolality, which results in degranulation of inflammatory cells and release of inflammatory mediators [5,6].

Diagnosis of EIB should not be based exclusively on self-reported symptoms [7–9] as they lack sensitivity and specificity [10–14]. Instead, EIB diagnosis should be objective and based on a fall in forced expiratory volume in 1 s (FEV_1) after an exercise challenge, or a surrogate for exercise such as eucapnic voluntary hyperpnoea (EVH) [7,9]. Exercise challenges are highly specific, but they lack sensitivity and thus the rate of false-negative diagnoses can be high [13,15]. Exercise challenges are also difficult to standardise due to changing environmental conditions and ventilatory responses, which determine the degree of EIB [15,16]. The EVH test

Abbreviations: EVH, eucapnic voluntary hyperpnoea; HIB, hyperpnoea-induced bronchoconstriction; EIB, exercise-induced bronchoconstriction; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; MVV, maximal voluntary ventilation; $\dot{V}_E$, minute ventilation; AUC, area under the curve; CV, coefficient of variation; SMC, smallest meaningful change.

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comprises 6 min of voluntary hyperpnoea using a dry gas and high minute ventilation ($\dot{V}_E$). Hyperpnoea-induced bronchoconstriction (HIB) is diagnosed when FEV_1 falls by ≥10% [17,18]. The EVH test can be tightly controlled, has high specificity and sensitivity for diagnosing EIB, and results in fewer false-negative diagnoses compared with exercise challenges [15,19–21]. It is therefore considered a superior bronchoprovocation challenge for identifying EIB [15,22].

The clinical utility of the EVH test critically depends on the extent to which it elicits a reproducible day-to-day fall in FEV_1. Reproducibility is determined by the measurement error and within-individual fluctuation, which may increase with longer time intervals [23]. However, few studies have examined the reproducibility of HIB elicited by EVH across different time intervals and using robust methods. Some studies failed to use appropriate statistical techniques to evaluate reproducibility [17], whereas others examined elite swimmers [14] who may have a unique EIB pathophysiology [24,25]. Price et al. [26] reported poor reproducibility for the fall in FEV_1 (95% limits of agreement: −10.7%–9.5%) after EVH in 32 individuals (6 with physician diagnosed asthma) with borderline HIB (~10% fall in FEV_1). The reproducibility of HIB elicited by EVH in individuals with physician diagnosed asthma and more severe HIB is therefore unknown.

Thus, the aim of the present study was to evaluate the short- (21 days) and long- (70 days) term test-retest reproducibility of HIB elicited by EVH in individuals with physician diagnosed asthma who were also positive for HIB during initial screening.

2. Methods

Following approval from the Nottingham Trent University Human Ethics Committee, two cohorts of 16 physically active (completing 4–6 h of aerobic exercise per week) males provided written informed consent to participate in a short-term (4 EVH tests each separated by 7 days) or long-term (3 EVH tests each separated by 35 days) study of HIB reproducibility. All participants were non-smokers and had no history of smoking. Each cohort comprised 8 control participants and 8 HIB-positive participants. Inclusion criteria for HIB-positive participants included physician diagnosis of asthma, a baseline FEV_1 >65% of predicted [17], and a ≥10% fall in FEV_1 following EVH [9]. On commencing the short-term study, HIB-positive participants were taking the following prescribed medication: N = 5, short acting β2 agonists; N = 1, combination of short acting β2 agonists and inhaled corticosteroids; N = 1, combination of short and long acting β2 agonists and inhaled corticosteroids; N = 1, combination of short acting β2 agonists, inhaled corticosteroids, and leukotriene modifiers. On commencing the long-term study, HIB-positive participants were taking the following prescribed medication: N = 5, short acting β2 agonists; N = 1 short acting β2 agonists and inhaled corticosteroids; N = 2, short and long acting β2 agonists and inhaled corticosteroids. Inclusion criteria for the HIB-positive group did not consider changes of medication prior to starting the study, but exclusion criteria included a change in medication during the study. Throughout the study, participants adhered to their usual habitual exercise regime and avoided strenuous exercise during the 48 h prior to testing [18].

3. Pulmonary function and EVH test

Baseline pulmonary function (forced vital capacity (FVC) and FEV_1) was assessed according to published guidelines [27] using a pneumotachograph (Pneumotrac, Vitalograph, Buckinghm, UK) as previously described [28,29].

For the 2 weeks prior to each EVH test, participants were free from any chest or upper respiratory tract infection [19]. On EVH test days participants abstained from caffeine and alcohol as they can influence asthma exacerbations [30,31], and arrived at the laboratory at least 2 h post-prandial. For each participant, EVH tests were performed at the same time of day. Participants with asthma ceased their medication prior to each EVH test (inhaled corticosteroids and leukotriene modifiers: 4 days; inhaled long acting β2 agonists: 2 days; anti-histamines: 2 days; inhaled short acting β2 agonists: the day of the test) [18,19].

The EVH test comprised 6 min of voluntary hyperpnoea at a target $\dot{V}_E$ of 85% of the predicted maximal voluntary ventilation (MVV) (30 × baseline FEV_1) [17,18]. Participants breathed through a flanged mouthpiece (Series 9060; Hans Rudolph, Missouri, USA) connected to a flow sensor (ZAN variable orifice pneumotach; Nspire Health, Oberthulba, Germany) that was calibrated using a 3 L syringe. Gas concentrations were measured using fast responding laser diode absorption spectroscopy sensors, which were calibrated using gases of known concentration (5% CO_2, 15% O_2, balance N_2; BOC, Guilford, UK), and ventilatory and pulmonary gas exchange variables were measured breath-by-breath (ZAN 600USB; Nspire Health) as previously described [28,29]. A two-way non-rebreathing valve (2700 Series; Hans Rudolph) was connected distally to the flow sensor and the inspiratory port was connected via a 1.2 m length of corrugated tubing (internal diameter: 35 mm) to a 150 L capacity Douglas bag. Participants inspired from the Douglas bag which was continuously filled with gases of known concentration (21% O_2, 5% CO_2, balance N_2; BOC) [32]. The inspired gas was at room temperature (19–21 °C) and of low humidity (<3%). During EVH, participants faced a computer monitor and received real-time visual feedback of $\dot{V}_E$, and end-tidal CO_2 was continuously monitored to ensure that isocapnia was maintained. After EVH, pulmonary function was assessed in duplicate at 3, 6 and 16 min, and the highest values recorded were used for subsequent analysis. After the EVH test, HIB-positive participants were supervised in the laboratory until their FEV_1 was within 10% of their baseline FEV_1.

4. Statistical analysis

The short- and long-term reproducibility studies were analysed separately using the Statistical Package for the Social Sciences (SPSS, Chicago, IL). Between-group comparisons (HIB-positive vs. control) for baseline FVC and FEV_1 were made using independent samples t-tests. One-way repeated measures ANOVA followed by Bonferroni adjusted pairwise comparisons was used to evaluate the within-group effects of day (short-term study: day 0, 7, 14, and 21; long-term study: day 0, 35, and 70) on baseline FVC and FEV_1. One-way repeated measures ANOVA followed by Bonferroni adjusted pairwise comparisons was used to evaluate the within-group effects of time after EVH (3, 6, and 16 min) on FVC and FEV_1. On all occasions there were no differences between these time points for FVC and FEV_1 and, therefore, the three values were averaged and used for further analyses, including reproducibility statistics. One-way repeated measures ANOVA followed by Bonferroni adjusted pairwise comparisons was used to evaluate the within-group effects of day on the average FVC and FEV_1 measured after EVH. In HIB-positive participants the area under the curve for $\%\Delta FEV_1$ during the 16 min period after EVH ($AUC_{0-16}\%\Delta FEV_1$) was calculated using the trapezoidal rule.

Day-to-day variation in baseline FVC and FEV_1, and the fall in FEV_1 after EVH, was calculated as the within-participant coefficient of variation (CV). Measurement error and reproducibility were calculated for FVC and FEV_1 measured before and after EVH. The same statistics were also calculated for the absolute change in FVC and FEV_1 from baseline to post-EVH. The smallest meaningful change was subsequently determined [33,34]. Statistical