Word count: 1258.

DIAGNOSING EXERCISE-INDUCED BRONCHOCONSTRICTION: OVER OR UNDER-DETECTION?

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Key words: Asthma, athletes, diagnosis, exercise-induced bronchoconstriction (EIB), indirect bronchoprovocation.

To the Editor:

Exercise-induced bronchoconstriction (EIB) refers to acute airway narrowing that occurs in association with physical activity and is prevalent in both elite and recreational athletes [1,2]. It is important to accurately detect EIB to reduce its potential impact on respiratory health and sporting performance [3 4], however diagnosis is clinically challenging due to the limited value of self-reported respiratory symptoms [5] and broad differential diagnosis associated with exertional breathing difficulty [6]. It is therefore recommended that EIB should be objectively confirmed via indirect bronchoprovocation prior to initiating treatment [7]. In this context, exercise challenge testing (EX) and eucapnic voluntary hyperpnoea (EVH) are the most commonly employed diagnostic tests, with a positive result most typically defined as a pre-post challenge reduction in lung function; i.e. ≥10% fall in FEV_1 [7]. However, the most appropriate diagnostic threshold currently remains unclear on the basis that the 'normative' airway response to EX appears to be mild bronchodilation (primarily due to withdrawal of vagal cholinergic tone) - whereas the highly provocative stimulus of EVH typically elicits bronchoconstriction [8]. Accordingly, to date, there remains a lack of consensus regarding the optimal or 'gold-standard' approach to assessment [9], which in turn, presents a potential for misdiagnosis; i.e. over and under-detection.

The primary aim of this study was therefore to compare the airway response to EX (conducted in a controlled dry environment) against an EVH challenge. An evaluation of current [7] and revised diagnostic thresholds [8] was undertaken to determine the impact of any proposed modification to EIB screening outcome. We hypothesised that the achieved ventilation and severity of bronchoconstriction would be greater following EVH in comparison to EX.

The study was conducted as a multi-site randomised trial. Following approval from local research ethics committees, sixty-three recreationally active individuals (≥5 hours endurance training per week) (male: n = 47) provided written informed consent. At the beginning of each visit, exertional respiratory symptoms and eosinophilic airway inflammation were assessed via interview and fractional exhaled nitric oxide (FeNO), respectively, followed by either an EX or EVH challenge. Spirometry was performed in triplicate at baseline and in duplicate at 3, 5, 7, 10, and 15-min post challenge. A positive

diagnosis for EIB was defined by ≥10% fall in FEV_1 at two consecutive time-points for both EX and EVH [7] and ≥15% fall in FEV_1 at one time-point for EVH [8] (for detailed overview of study methodology refer to online supplement).

Fourteen participants (22%) had a prior diagnosis of asthma +/- EIB. Despite this, all participants had normal resting lung function with no evidence of airflow limitation (FEV_1 predicted >80% and FEV_1/FVC >70% predicted). Over half of the cohort (63%) reported exertional respiratory symptoms, and twenty-six (41%) had elevated FeNO (>25ppb). Clinical characteristics and baseline lung function are presented in Table 1.

Fifty-eight (92%) and forty-four (70%) participants achieved a $\dot{V}_E$ ≥60% predicted MVV (i.e. the accepted minimal ventilatory load for a valid test) for EVH and EX, respectively. Although power output during EX (260 ± 57 W) was lower than the calculated target (323 ± 92 W; P<0.01), all participants achieved a mean heart rate >80% predicted maximum (162 ± 11 beats.min^{-1}). Despite this, $\dot{V}_E$ for EX (93 ± 19 L.min^{-1}) was lower than EVH 106 ± 22 L.min^{-1}, P<0.01; Table 1).

The mean fall in FEV_1 was greater following EVH (-7.9 ± 6.9%) in comparison to EX (-1.9 ± 7.1; P<0.01), with a reduction in FEV_1 observed following EVH in almost all participants (94%). In contrast, EX elicited bronchodilation in over half of the cohort (53%). Thirteen (21%) had a fall in FEV_1 ≥10% following EVH, of which five (8%) were positive to EX. Importantly, none were positive to EX and negative to EVH (Figure 1a). Furthermore, in those with ≥10% fall in FEV_1, the mean reduction in lung function (i.e. severity of EIB) was greater following EVH (-19 ± 7%) in comparison to EX (-11 ± 9%; P<0.01). Nine (14%) had a ≥15% fall in FEV_1 post EVH, of which four (6%) were positive to EX. Of note, in those who failed to achieve 60% MVV, two were still positive to EVH whereas none were positive to EX. Although a positive correlation was observed between EX and EVH (r_s = 0.46, p <0.01) the mean bias was 6.1% with wide limits of agreement (LOA) (-5.3 to +17.5 %) (Figure 1b). Similarly, a positive correlation was observed in those with asthma +/- EIB (r = 0.73, p <0.05) (mean bias: 7.5%; LOA: -6.7 to + 22.7%). Importantly, a similar pattern of response was observed for the forty-four participants (70%) who achieved ≥60% MVV for both tests. The mean fall in FEV_1 was greater

following EVH (-8.3 ± 7.4%) in comparison to EX (-2.3 ± 7.8; P<0.01). Eleven (25%) had a fall in FEV_1 ≥10% following EVH, of which five (18%) were positive to EX. Seven (16%) had a ≥15% fall in FEV_1 post EVH, of which four (6%) were positive to EX. Sensitivity and specificity for EVH and FeNO (to predict a positive EX test) are presented (for the entire cohort) in Tables S2 and S3, respectively.

The present study indicates that the proportion of individuals who meet the diagnostic criteria for EIB is consistently greater following EVH in comparison to a controlled laboratory EX test in a standardised dry environment. Applying a 10% fall in FEV_1 cut-off for EVH increases diagnostic sensitivity, whereas a 15% fall in FEV_1 improves diagnostic specificity. The observed disparity in screening outcome has implications for the clinical application of EVH when utilised as a surrogate airway challenge for EX and highlights a potential risk of over and under-detection depending on test selection when applying current guidelines [7].

The airway response to any indirect bronchoprovocation challenge is directly related to the potency of the airway stimulus delivered. In the context of EX and EVH, provocation is primarily driven by $\dot{V}_E$ and the water content of inspired air. However, aligning $\dot{V}_E$ for EX and EVH is problematic from a methodological standpoint on the basis that $\dot{V}_E$ increases over time with EX, whereas EVH involves an immediate square-wave rise with sustained hyperpnoea throughout the challenge. In addition, the relative humidity of medical-grade gas utilised for EVH was substantially lower (EX: 25% RH vs. EVH: 2% RH) despite conducting EX in a controlled environment in accordance with current ATS recommendations (<10 mg H_2O/L) [7]. It is important to highlight that a warm-up prior to EX was included in the present study (albeit low intensity without a rest period), and whilst speculative, it is possible for a refractory period to have occurred in some participants. Taken together these factors likely explain the observed disparity in EIB prevalence between tests (EX: 8% vs. EVH: 21%). Finally, although employing a revised threshold for EVH [8] contributed to improved diagnostic agreement (EX: 8% vs. EVH: 14%) - one participant with a mild positive FEV_1 fall post EX (~10%) remained undetected. Of note, this individual did not report exertional respiratory symptoms (i.e. entirely asymptomatic) and would therefore only be detected via widespread screening.

Our findings indicate that the proportion of individuals who meet the diagnostic criteria for EIB is consistently greater following EVH in comparison to EX. A pragmatic solution for practitioners utilising EVH to screen athletes may be to apply a 10% fall in FEV_1 cut-off to ensure no EIB cases are missed, whereas a 15% fall in FEV_1 cut-off may increase the 'clinical' relevance in athletes presenting with exertional breathing difficulty. Further population-based research evaluating the normative response to indirect bronchoprovocation in this setting remains a priority.

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FUNDING STATEMENT

Nil relevant.

CONFLICT OF INTEREST

The authors have no real or perceived conflict of interest in respect of this manuscript.

CONTRIBUTION STATEMENT

All authors were involved in the conception and design of the study. AJ and HA collected and interpreted the data. All authors were involved with drafting and critical revision of the manuscript and final approval of the version to be published.

GUARANTOR STATEMENT

OJP and JD confirm full responsibility for the content of the manuscript, including data and analysis.

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Table 1. Participant clinical characteristics and airway response to EX and EVH.

Variables							
Sex (M:F)	47	:	16				
Age (years)	32	±	11				
Height (cm)	177	±	11				
Weight (kg)	74	±	12				
BMI ($kg \bullet m^{-2}$)	24	±	3				
Training ($hrs \bullet wk^{-1}$)	9	±	4				
Physician diagnosed asthma +/- EIB	14/63 (22%)						
Inhaler therapy:	14/14 (100%)						
Short-acting beta-2-agonist (SABA)	12/14 (86%)						
Inhaled corticosteroid (ICS)	1/14 (7%)						
SABA + ICS	1/14 (7%)						
Exertional respiratory symptoms:	43/63 (67%)						
Cough	27/63 (43%)						
Excessive mucus production	22/63 (35%)						
Wheeze	18/63 (29%)						
Chest tightness	11/63 (17%)						
Dyspnoea	9/63 (14%)						
	EVH			**EX**			**P-value**
FEV_1 (L)	4.07	±	0.73	4.05	±	0.73	0.25
FEV_1 predicted (%)	103.9	±	11.3	103.6	±	11.1	0.42
FVC (L)	5.11	±	1.08	5.10	±	1.07	0.46
FVC predicted (%)	108.9	±	13.0	108.6	±	13.3	0.53
FEV_1/FVC (%)	80.2	±	7.2	80.1	±	6.7	0.70
PEF ($L.min^{-1}$)	576.1	±	93.6	575.7	±	92.9	0.89
PEF predicted (%)	107.6	±	15.3	107.5	±	15.3	0.86
Predicted min ventilation ($L.min^{-1}$)	142	±	26	142	±	25	0.28
Achieved min ventilation ($L.min^{-1}$)	106	±	22	93	±	19	<0.01*
Achieved min ventilation (%)	75	±	12	67	±	16	<0.01*
Average fall in FEV_1 (%)	-7.9	±	6.9	-1.9	±	7.0	<0.01*
EIB positive (≥10% fall in FEV_1)	13/63 (21%)			5/63 (8%)			<0.01*
EIB positive (≥15% fall in FEV_1)	9/63 (14%)			2/63 (2%)			<0.01*
FeNO (ppb)	20 (5-162)			18 (5-155)			0.29
FeNO (≥25ppb)	22/63 (35%)			24/63 (37%)			0.82

Data presented as mean ± SD and ratio (percentage). *Indicates difference between EVH and EX ($P<0.05$). Non-normally distributed data presented as median score (range). Definitions of abbreviations: BMI, body mass index; EVH, eucapnic voluntary hyperpnea; EX, exercise challenge test; FEV_1, Forced expiratory volume in 1^{-s}; FVC, Forced vital capacity; PEF, Peak expiratory flow; MVV, Maximum voluntary ventilation; FeNO, Fractional exhaled nitric oxide.

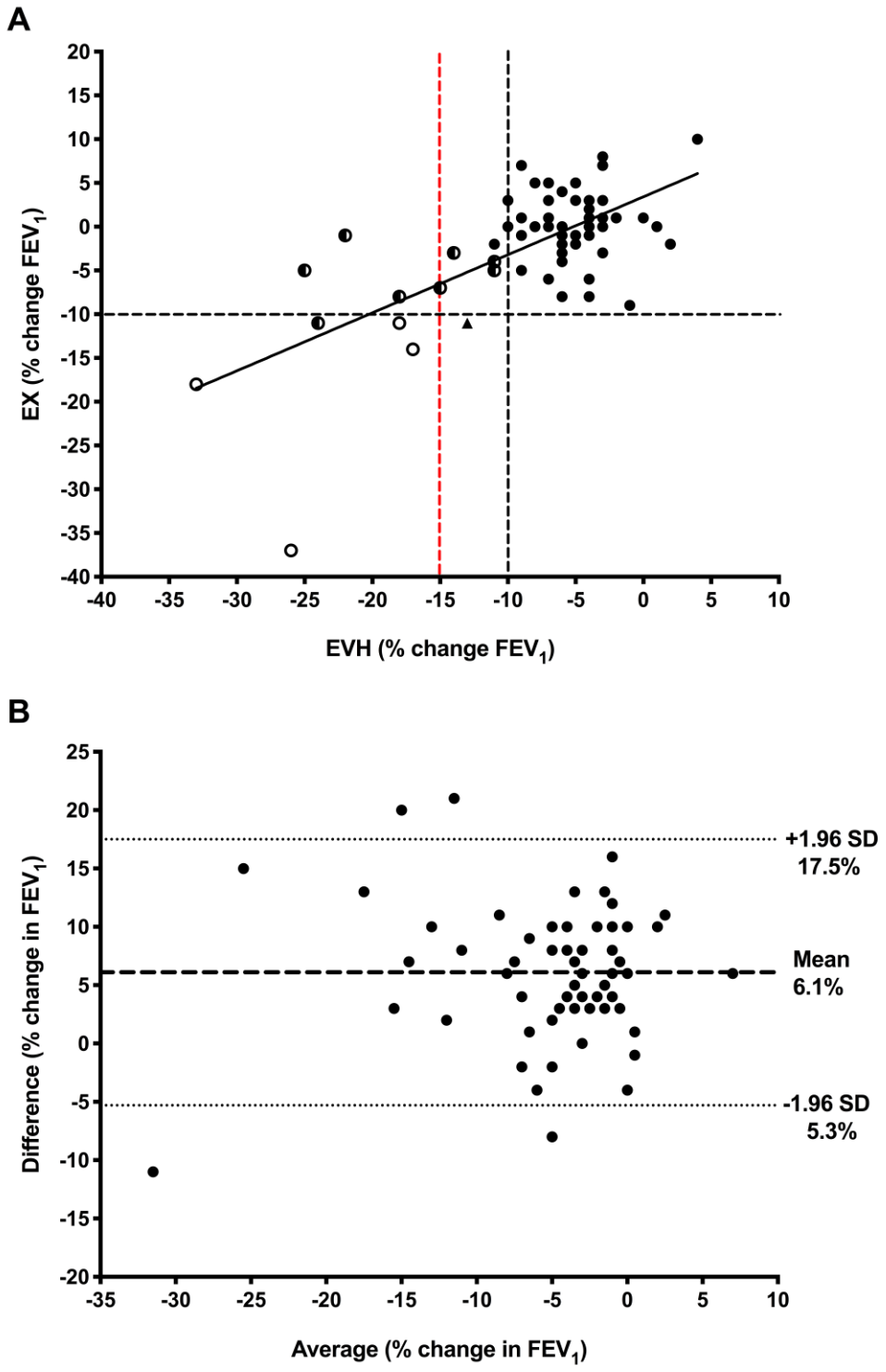
A
EX (% change FEV1)
EVH (% change FEV1)
B
Difference (% change in FEV1)
Average (% change in FEV1)
+1.96 SD
17.5%
Mean
6.1%
-1.96 SD
5.3%

Figure 1.

FIGURE HEADERS

Figure 1a. Airway response following bronchoprovocation.

EX + EVH negative (*closed circles*); EX + EVH positive (*open circles*); EX negative + EVH positive (*split circles*); EX positive + EVH negative (*closed triangle*). Diagnostic thresholds: Black vertical line and black horizontal line (≥10% fall in FEV_1 at two consecutive time-points); Red vertical line (15% fall in FEV_1 at one time-point).

Figure 1b. Bland-Altman plot of the change in FEV_1 post EX and EVH challenges.