Exercise-induced bronchoconstriction and bronchodilation: investigating the effects of age, sex, airflow limitation and FEV_1

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Exercise-induced bronchoconstriction (EIBc) and bronchodilation (EIBd) occur after exercise, and are influenced by increasing age, lower FEV_1 % pred and airflow limitation. Female sex influences EIBc but not EIBd. https://bit.ly/3nDGrwm

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Abstract

Exercise-induced bronchoconstriction (EIBc) is a recognised response to exercise in asthmatic subjects and athletes but is less well understood in an unselected broad population. Exercise-induced bronchodilation (EIBd) has received even less attention. The objective of this study was to investigate the effects of age, sex, forced expiratory volume in 1 s (FEV_1) and airflow limitation (FEV_1/forced vital capacity (FVC) <0.7) on the prevalence of EIBc and EIBd.

This was a retrospective study based on incremental cardiopulmonary exercise testing on cycle ergometry to symptom limitation performed between 1988 and 2012. FEV_1 was measured before and 10 min after exercise. EIBc was defined as a percentage fall in FEV_1 post-exercise below the 5th percentile, while EIBd was defined as a percentage increase in FEV_1 above the 95th percentile.

35 258 subjects aged 6–95 years were included in the study (mean age 53 years, 60% male) and 10.3% had airflow limitation (FEV_1/FVC <0.7). The lowest 5% of subjects demonstrated a ⩾7.6% fall in FEV_1 post-exercise (EIBc), while the highest 5% demonstrated a >11% increase in FEV_1 post-exercise (EIBd). The probability of both EIBc and EIBd increased with age and was highest in females across all ages (OR 1.76, 95% CI 1.60–1.94; p<0.0001). The probability of EIBc increased as FEV_1 % pred declined (<40%: OR 4.38, 95% CI 3.04–6.31; p<0.0001), with a >2-fold increased likelihood in females (OR 2.31, 95% CI 1.71–3.11; p<0.0001), with a trend with airflow limitation (p=0.06). The probability of EIBd increased as FEV_1 % pred declined, in the presence of airflow limitation (OR 1.55, 95% CI 1.24–1.95; p=0.0001), but sex had no effect.

EIBc and EIBd can be demonstrated at the population level, and are influenced by age, sex, FEV_1 % pred and airflow limitation.

Introduction

Physicians, teachers and parents supervising athletic activity in children are often faced with complaints of breathlessness, wheezing, light-headedness and paraesthesia after high-intensity activity. The production of carbon dioxide dramatically falls after exercise cessation. Continued hyperventilation after exercise cessation leads to hypocapnia accompanied by transient cerebral ischaemia and syncope. Whether such children truly have exercise-induced bronchoconstriction (EIBc) or asthma remains a diagnostic challenge without spirometry.

Bronchoconstriction following strenuous muscular activity is common in children, who are uniquely prone because their lungs and airways are small and immature [1]. With reduced elastic recoil, even a small degree of airway smooth muscle contraction reduces airflow to a much greater extent than in adults. This probably explains why field studies on young children form the bulk of the reported experience in

exercise-induced asthma or EIBc. JONES *et al.* [2] formally described this phenomenon in children in 1962. In 1968, severe EIBc was also noticed in an 18-year-old Olympic Gold Medallist swimmer [3].

The measurement of spirometry before, during and following exercise has been popularised. Although less sensitive than other spirometric indices, forced expiratory volume in 1 s (FEV_1) is the measurement most used [4–6] and a 10% fall post-exercise is the current guideline recommended threshold [7]. Studies on EIBc have been in highly selected populations of asthmatic subjects, or athletes, with minimal data in normal subjects. From such studies it is difficult to infer the effects of exercise on airway responses in a broad population with other common cardiorespiratory conditions.

For several decades at McMaster University Medical Centre, spirometry has been measured prior to and 10 min after maximum incremental cardiopulmonary exercise testing (CPET) on cycle ergometry. The motivation of this study was to investigate the behaviour of the airways following CPET in order to provide a broader experience of airway responses than any previously reported. FEV_1 was measured before and 10 min after incremental exercise to symptom-limited capacity in all subjects. The frequency of EIBc and exercise-induced bronchodilation (EIBd) could then be identified in specifically defined subgroups. The contributions of age, sex and baseline FEV_1 % pred, with and without airflow limitation (FEV_1/forced vital capacity (FVC) <0.7), on the frequency of EIBc and EIBd were investigated, alone and with interactions.

Methods

Study design

This was a retrospective study based on data collected from sequential patients referred for clinical exercise testing at McMaster University Medical Centre (Hamilton, ON, Canada) between 1988 and 2012. Electronic data download after 2012 was not technically feasible due to a change in the software used. All subjects with pre- and post-exercise FEV_1 measurements were included. There were no exclusions. The most common indication for exercise testing was predominantly for the assessment of exercise-induced symptoms of chest pain (25%), dyspnoea (12%), pre-cardiac rehabilitation (10%) and post-myocardial infarction (7%), and suspected exercise-induced asthma (3%) and other disorders (congenital heart disease (3%), cystic fibrosis (2%) and chronic obstructive pulmonary disease (COPD) (2%)).

Study procedures

Prior to exercise, risks of exercise were explained, and informed consent was obtained for exercise testing and the use of the data collected for audit and research purposes. The indication for exercise was recorded and current drug medication collected. Before exercise, muscle strength using maximum volitional contraction of the inspiratory and expiratory muscles against an occluded airway at residual volume and total lung capacity, seated bench press and row, and knee extension (quadriceps) and flexion (hamstrings) using maximum contraction against hydraulic resistance with quasi-isokinetic characteristics. Spirometry was measured with maximum expiratory and inspiratory manoeuvres from total lung capacity to residual volume yielding FVC and FEV_1, peak expiratory flow rates and forced expiratory flow at 25%, 50% and 75% of expired vital capacity. Peak inspiratory flow rate and forced inspiratory flow at 25%, 50% and 75% were also measured. Single-breath lung volume (communicating lung volume), diffusing capacity of the lung for carbon monoxide and transfer coefficient of the lung for carbon monoxide were measured. Haemoglobin, carboxyhaemoglobin, arterial oxygen saturation and arterialised capillary blood gases were also measured.

CPET involved incremental increases in power on a servo-controlled upright cycle ergometer to symptom-limited capacity. The stepwise increase in power output was 100 kilopond metres (kpm) (16 W). During exercise, oxygen uptake, carbon dioxide output, respiratory exchange ratio (respiratory quotient), ventilation, tidal volume, respiratory rate, heart rate, blood pressure and ECG were monitored. After exercise, ECG monitoring continued for 10 min, followed by repeat spirometry.

Predicted normal values for FEV_1 and maximum power output

The prediction equation for normal values was derived in the same population using the following criteria: never-smoker, no prescription medications, no past medical history and body mass index 20–30 $kg \cdot m^{-2}$, but an additional requirement of achieving normal capacity to exercise without excessive symptoms, *i.e.* there was no disability or symptom handicap. The equations derived followed standard allometric principles: 1) a positive acceleration of FEV_1 and maximum power output (MPO) with height; 2) proportionately higher values in males than females of the same height; 3) a proportionate decline in FEV_1 in both sexes after the age of 35 years; and 4) a proportionate increase as age increases to skeletal maturity at age 20 years. The equations derived are: FEV_1=0.92×height $(m)^{2.39}$×(1.129 in males)×(1−(0.0076×age

>35 years))×(1−(0.012×age <20 years)) and MPO=328×height (m)$^{2.10}$×(1.29 in males)×(1−(0.0085×age >35 years))×(1+(0.0034×age <20 years)).

Study objectives

Four main questions were investigated: what was the probability of EIBc and EIBd 1) at each decade of age in females and males, 2) in those with an exercise capacity achieved of <50%, 50–80% and >80% predicted normal in females and males, 3) in those with FEV_1 % pred <50%, 50–80% and >80% with and without airflow limitation (FEV_1/FVC <70%), and 4) in terms of the interaction between sex, airflow limitation (FEV_1/FVC <70%) and FEV_1 % pred <50%, 50–80% and >80%?

Statistical analysis

FEV_1 was expressed as a percentage of the pre-exercise value. No assumption as to normal parametric distribution was assumed. The 5th and 95th percentiles were directly identified. EIBc was assumed if the FEV_1 post-exercise was <5th percentile. EIBd was assumed if the FEV_1 post-exercise was >95th percentile. Thus, the null hypothesis for both EIBc and EIBd was a probability of 0.05. The probabilities of both EIBc and EIBd were calculated for each defined population group. Odds ratios were calculated using logistic regression. The reference population group was that group with the lowest rates of EIBc and EIBd observed.

Results

Study population

35 258 subjects aged 6–95 years were included in the study (mean age 53 years, 60% male) and 10.3% had airflow limitation (FEV_1/FVC <0.7). The distribution of FEV_1 post-exercise expressed as percentage of FEV_1 before exercise is shown in figure 1. The 5th percentile was 92.4%; the 95th percentile was 111.1%. 1771 subjects were classified as EIBc and 1861 subjects were classified as EIBd. Anthropometrics and baseline respiratory measures are shown in table 1, and physiological parameters at MPO are shown in table 2. Subjects with EIBc and EIBd had a lower FEV_1 and a greater proportion had airflow limitation at baseline, with 34% considered to be normal in both groups (no history of myocardial infarction, COPD or asthma, normal spirometry and normal exercise capacity).

Effects of sex and ageing

The probabilities of EIBc and EIBd are shown in figure 2a and b, respectively. Females had an increased likelihood of EIBc compared with males (females: OR 1.76, 95% CI 1.60–1.94; p<0.0001). The probability of EIBc in both males and females was lowest in those aged 40–50 years (males 3.2% and females 4.7%) and increased subsequently, reaching a peak of 10.3% in females and 7.5% in males. Except for those aged <10 years, the probabilities were always greater in females than males.

In contrast to EIBc, females had no increased likelihood of EIBd over the whole age range compared with males (females: OR 1.04, 95% CI 0.95–1.15; p=0.38). The probability of EIBd in males was lowest in those aged 10–20 years (3.2%) and in females in those aged 30–40 years (3.2%). For males and females

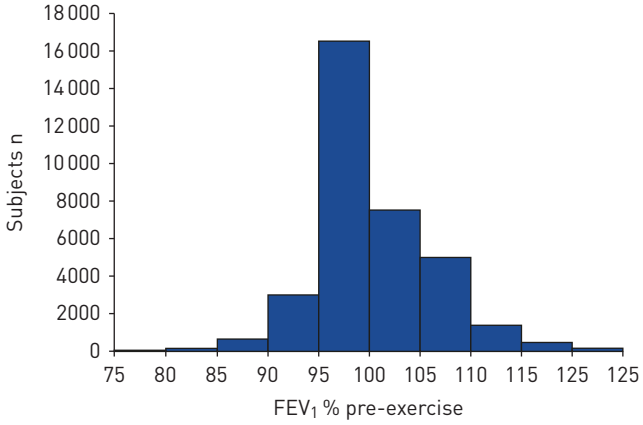

FIGURE 1 Distribution of changes in forced expiratory volume in 1 s (FEV_1) post-exercise as a percentage of pre-exercise.

TABLE 1 Demographics and baseline physiology

	Neither EIBc nor EIBd	EIBc	EIBd	p-value
Subjects	31 626	1771	1861	
Age years	52.7 (52.47–52.86)	54.4 (53.56–55.33)	55.9 (55.11–56.69)	<0.0001
Male %	60.70 (60.25–61.33)	47.24 (44.85–49.64)	59.17 (56.98–61.37)	<0.0001
Height m	1.69 (1.69–1.69)	1.66 (1.65–1.66)	1.67 (1.67–1.68)	<0.0001
Weight kg	78.8 (78.58–78.99)	75.3 (74.37–76.16)	77.6 (76.74–78.47)	<0.0001
BMI kg·m^{-2}	27.4 (27.35–27.47)	27.3 (27.00–27.54)	27.5 (27.24–27.75)	0.4441
FEV_1 L	2.79 (2.78–2.80)	2.33 (2.29–2.37)	2.30 (2.26–2.34)	<0.0001
FEV_1 % pred	92.6 (92.39–92.80)	83.8 (82.78–84.88)	80.2 (79.20–81.20)	<0.0001
FVC L	3.48 (3.47–3.49)	2.98 (2.93–3.02)	3.02 (2.97–3.06)	<0.0001
FVC % pred	103.9 (103.64–104.08)	94.7 (93.65–95.75)	94.2 (93.18–95.14)	<0.0001
FEV_1/FVC %	80.07 (79.97–80.16)	77.66 (77.14–78.18)	75.78 (75.24–76.33)	<0.0001
FEV_1/FVC <0.7 %	0.09 (0.09–0.09)	0.18 (0.16–0.20)	0.22 (0.20–0.24)	<0.0001
D_{LCO} mL·mmHg^{-1}·min^{-1}	22.50 (22.43–22.57)	20.17 (19.85–20.50)	21.14 (20.83–21.45)	<0.0001
V_A L	5.20 (5.18–5.21)	4.60 (4.54–4.66)	4.96 (4.90–5.02)	<0.0001
K_{CO} mL·mmHg^{-1}·min^{-1}·L^{-1}	4.39 (4.38–4.40)	4.44 (4.39–4.49)	4.35 (4.30–4.40)	0.0317
Quadriceps strength kg	39.79 (38.83–40.76)	42.29 (41.37–43.20)	46.84 (46.62–47.07)	<0.0001
MIPS cmH_2O	65.73 (64.32–67.14)	68.83 (67.48–70.19)	75.46 (75.13–75.80)	<0.0001
MEPS cmH_2O	97.30 (95.44–99.16)	99.41 (97.71–101.11)	107.37 (106.95–107.79)	<0.0001

Data are presented as n or mean (95% CI), unless otherwise stated. EIBc: exercise-induced bronchoconstriction; EIBd: exercise-induced bronchodilation; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V_A: alveolar volume; K_{CO}: transfer coefficient for carbon monoxide; MIPS: maximum inspiratory pressure strength; MEPS: maximum expiratory pressure strength. p-values calculated using ANOVA.

there was a gradual increase in EIBd with age up to 8.4% in females and 7.5% in males for those aged >80 years. Importantly, the highest probability of EIBd in females was in those aged <10 years.

Effects of sex and MPO

EIBc increased in a positively accelerating manner as the MPO achieved decreased, with females experiencing EIBc to a greater extent than males (females: OR 1.67, 95% CI 1.49–1.87; p<0.0001) (figure 3a). EIBd also increased substantially as the MPO achieved decreased in females and males, but with both being similarly affected (females: OR 0.98, 95% CI 0.8–1.11; p=0.76) (figure 3b).

Effects of FEV_1 % pred with and without airflow limitation

The probability of EIBc increased as FEV_1 decreased and was not different in the presence of airflow limitation (airflow limitation: OR 1.06, 95% CI 0.86–1.30; p=0.59) (figure 4a). There was a greater than

TABLE 2 Physiological assessment at peak exercise during incremental cardiopulmonary exercise testing

	Neither EIBc nor EIBd	EIBc	EIBd	p-value
Ventilation L·min^{-1}	58.34 (58.08–58.59)	50.44 (49.42–51.46)	51.76 (50.76–52.77)	<0.0001
Respiratory rate breaths·min^{-1}	32.08 (31.99–32.17)	32.88 (32.49–33.27)	31.59 (31.24–31.95)	<0.0001
Tidal volume L	1.85 (1.84–1.86)	1.56 (1.53–1.59)	1.66 (1.63–1.69)	<0.0001
Tidal volume % VC	53.09 (52.97–53.21)	52.59 (52.07–53.12)	55.19 (54.62–55.75)	<0.0001
MPO kpm·min^{-1}	805.90 (802.21–809.59)	680.12 (665.25–694.99)	711.58 (697.11–726.05)	<0.0001
MPO % pred	81.91 (81.64–82.17)	75.79 (74.61–76.98)	76.22 (75.11–77.34)	<0.0001
V'_{O_2} L·min^{-1}	1.65 (1.64–1.65)	1.42 (1.38–1.45)	1.45 (1.42–1.48)	<0.0001
V'_{CO_2} L·min^{-1}	1.79 (1.78–1.80)	1.50 (1.47–1.54)	1.56 (1.53–1.60)	<0.0001
Respiratory quotient	1.08 (1.08–1.08)	1.05 (1.05–1.06)	1.07 (1.06–1.07)	<0.0001
S_{aO_2} %	95.61 (95.58–95.64)	95.13 (94.99–95.27)	95.14 (95.01–95.28)	<0.0001
P_{aO_2} mmHg	85.24 (85.00–85.49)	82.71 (81.67–83.75)	82.70 (81.71–83.69)	<0.0001
P_{ETCO_2} mmHg	35.98 (35.92–36.04)	35.80 (35.57–36.03)	35.96 (35.68–36.23)	0.377

Data are presented as mean (95% CI), unless otherwise stated. EIBc: exercise-induced bronchoconstriction; EIBd: exercise-induced bronchodilation; VC: vital capacity; MPO: maximum power output; V'_{O_2}: oxygen uptake; V'_{CO_2}: carbon dioxide production; S_{aO_2}: arterial oxygen saturation; P_{aO_2}: arterial oxygen tension; P_{ETCO_2}: end-tidal carbon dioxide tension. p-values calculated using ANOVA.

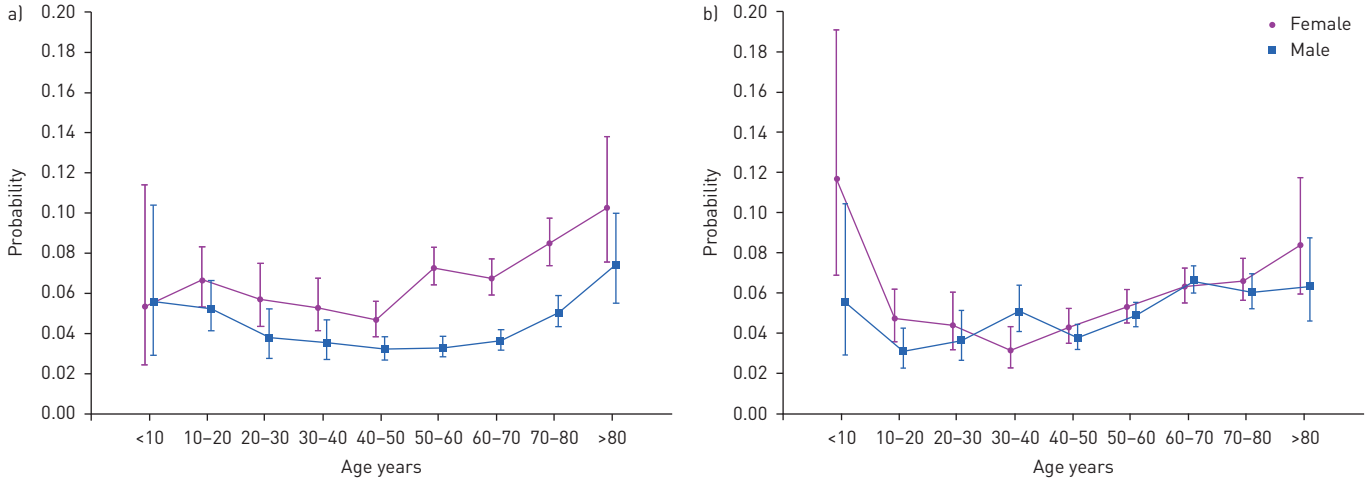

FIGURE 2 Probability of a) exercise-induced bronchoconstriction and b) exercise-induced bronchodilation based on age and sex. Data are presented as mean (95% CI).

4-fold increased likelihood of EIBc as FEV_1 % pred decreased from >80% to <40% (OR 4.38, 95% CI 3.04–6.31; p<0.0001).

The probability of EIBd increased as FEV_1 decreased and was ~50% greater in the presence of airflow limitation (airflow limitation: OR 1.51, 95% CI 1.23–1.86; p<0.0001) (figure 4b). The effect of airflow limitation was most noticeable in those with FEV_1 >80% and 40–60% predicted.

Effects of sex, airflow limitation and FEV_1 % pred

The probability of EIBc increased in a positively accelerating manner as FEV_1 % pred declined, with a greater than doubling increased likelihood in females (OR 2.31, 95% CI 1.71–3.11; p<0.0001) (figure 5a and b). The effect of the presence of airflow limitation did not reach statistical significance (OR 1.34, 95% CI 0.99–1.81; p=0.06).

The probability of EIBd increased as FEV_1 % pred declined, with no effects of sex (female: OR 1.12, 95% CI 0.90–1.40; p=0.32) (figure 5c and d). The presence of airflow limitation increased the probability of EIBd (OR 1.55, 95% CI 1.24–1.95; p=0.0001).

Discussion

This is the largest study to date to describe EIBc and EIBd after CPET in a real-world group of subjects, independent of any diagnostic labels. In 35 258 subjects, the lowest 5% (1771 subjects) demonstrated a ⩾7.6% fall in FEV_1 post-exercise (EIBc), while the highest 5% (1865 subjects) demonstrated a >11%

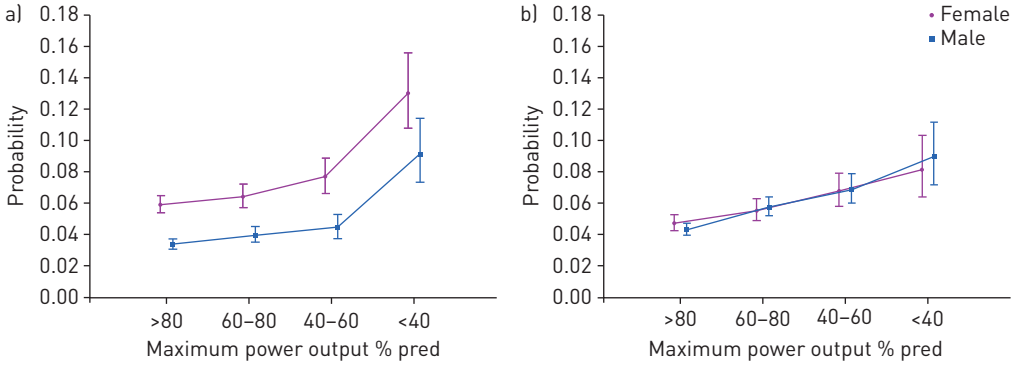

FIGURE 3 Probability of a) exercise-induced bronchoconstriction and b) exercise-induced bronchodilation based on maximum power output and sex. Data are presented as mean (95% CI).

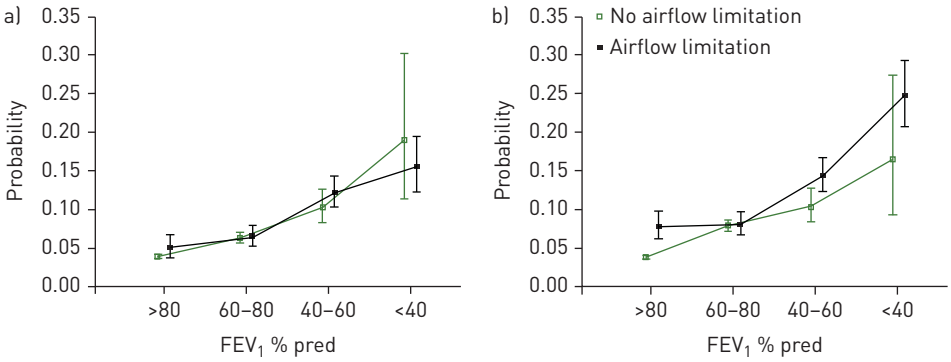

FIGURE 4 Probability of a) exercise-induced bronchoconstriction and b) exercise-induced bronchodilation based on forced expiratory volume in 1 s (FEV_1) % pred and the presence of absence of airflow limitation (FEV_1/forced vital capacity <0.7). Data are presented as mean (95% CI).

increase (EIBd). The main finding was that the probability of EIBc increased with increasing age, female sex, and lower MPO % pred and lower FEV_1 % pred pre-exercise. The probability of EIBd also increased with increasing age, and lower MPO % pred and FEV_1 % pred, but there was no effect of female sex. Furthermore, the presence of airflow limitation increased the likelihood of EIBd, but did not quite reach statistical significance for EIBc (p=0.06).

Our findings need to be understood in the context of the current postulated mechanisms of EIBc. The mechanism of EIBc is most commonly thought to be due to the osmotic effects of inhaling dry or cold air at high rates of ventilation, resulting in mast cell degranulation and the release of leukotrienes into the

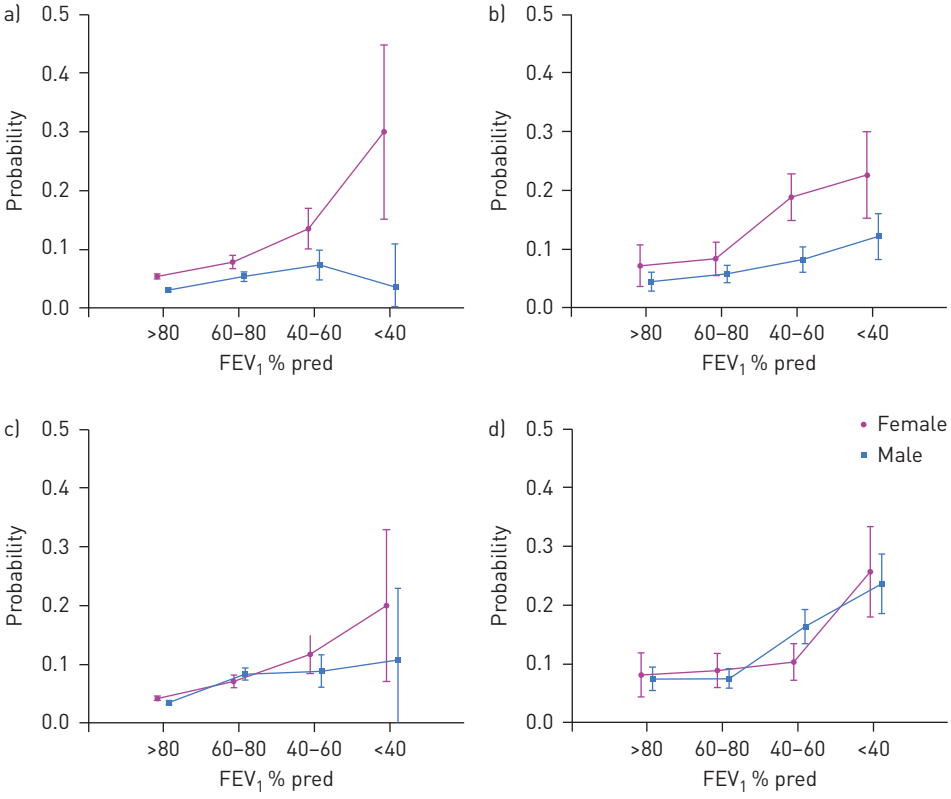

FIGURE 5 Probability of a, b) exercise-induced bronchoconstriction and c, d) exercise-induced bronchodilation based on sex, forced expiratory volume in 1 s (FEV_1) % pred and airflow limitation (FEV_1/forced vital capacity <0.7): a, c) no airflow limitation and b, d) airflow limitation. Data are presented as mean (95% CI).

airways [8–13]. However, alternative explanations include hypersensitivity of sensory nerves, autonomic imbalance [14] between the β_2-adrenoceptors and M_3 muscarinic receptors, and airway epithelial shedding and damage [15–17]. First, we did not find higher rates of ventilation and peak exercise in EIBc or EIBd. In contrast, we found both groups had lower maximum ventilation in EIBc and EIBd (table 2). Second, all subjects performed CPET in the same room, under the same temperature (24°C) and humidity (45% relative humidity), hence these were constant for all subjects. In asthmatic subjects, an important component of airway responses is the underlying level of airway responsiveness, which for any given level of ventilation, thermal or osmotic stimulus, the response would change based on airway reactivity [18]. Unfortunately, we do not have data on methacholine airway hyperreactivity in these subjects. Third, we are not aware of sex differences in β_2-adrenoceptors, M_3 muscarinic activity and mast cell function in humans. Sex differences in peripheral vascular adrenergic receptors have been reported [19]. Oestradiol, progesterone and testosterone receptors have been found to be expressed on mast cells in animal models and human tissue, but with no evidence of differential effects to stimulation based on sex [20–23]. Androgens modulate T-helper type 2 inflammation in murine asthma models [24], by attenuating type 2 innate lymphoid cells [25] and downstream interleukin (IL)-5 [26] and IL-17 [27].

However, sex differences in EIBc were consistently found across all age groups and did significantly increase with age, with a significant further increase even in females aged >50 years (figure 2a). This suggests loss of oestrogen after menopause or the presence of androgens in males might be implicated [28]. We also speculate that increased sensitivity of the sensory afferent nerves may influence an exaggerated activity of parasympathetic efferent nerves and airway smooth muscle as part of a reflex arc [29, 30]. To support this hypothesis, we have previously demonstrated exaggerated and heightened cough responses to inhaled capsaicin which are greatest in female asthmatic subjects [31]. Furthermore, bronchoconstriction further sensitises airway nerves [32]. Leukotriene D_4 [33], neurokinin [34] and prostaglandin D_2 [35] release have all been implicated in animal models. This may also explain why a lower FEV_1 % pred may increase the likelihood of EIBc. It must be noted that the increased respiratory drive during exercise is likely to also activate rapidly activating receptors rather than just the chemically sensitive c-fibres. Exactly how and why exercise would sensitise c-fibres and/or rapidly activating receptors more in females compared with males, and subsequently result in increased parasympathetic activity and bronchoconstriction, needs further evaluation.

The sex differences that we have shown over the age ranges and at different degrees of FEV_1 % pred, with and without airflow limitation, have not been previously reported. The prevalence of EIBc in athletes varies significantly depending on the population studied. In Olympians it has been estimated as 8% [36], but in higher risk athletes such as swimmers and cold-air athletes the range is considerably larger, between 25% and 75% [37–40]. A recent systematic review of 60 studies evaluating EIBc found an overall prevalence of 23% of EIBc in athletes [41]. However, only 15 studies, with a total of 2058 athletes, reported sex differences. In contrast to our study, the prevalence was slightly greater in males (17%) compared with females (13%), but no statistical difference between EIBc and sex was demonstrated.

In comparison, EIBd is even more poorly recognised and understood, but we demonstrated a significant >11% improvement in FEV_1 in our study with increasing age, worsening FEV_1 % pred and the presence of airflow limitation. EIBd has previously been studied in small numbers of subjects. In 1959, Capel and Smart [42] showed a 24% increase (range 3% to 52%) in FEV_1 during exercise in patients with obstructive lung disease. FEV_1 returned to baseline 5 min after exercise cessation. Gelb *et al.* [43] reported a 20% increase in FEV_1 during exercise in seven asthmatic males and proposed that stretching of the airway wall during exercise releases the products of cyclooxygenase that play a role in EIBd. Deep inspiration is also known to be bronchoprotective [44], and as the ventilation and lung volumes increase with exercise, there is potentially more efficient transport of surfactant throughout the alveolar space and terminal airways [45–47]. This decreases dynamic compliance and overall airway resistance.

From the perspective of the autonomic nervous system, every exercising subject faces changing cholinergic and adrenergic activity. In anticipation of exercise, the parasympathetic tone decreases and adrenergic effects then increase with increasing power. In recovery, these effects recede. In this context, EIBc may be due to increased cholinergic activity or β_2-receptor desensitisation by the excessive adrenergic activity during exercise. This mechanism, although postulated with excessive β_2-agonist use [48], has not been investigated in the context of exercise. In contrast, in EIBd there is persistence of adrenergic and anticholinergic activity, and this might be predicted in those subjects whose heart rate remains high. However, although heart rate was recorded, data was not collected electronically and the potential for further analysis in these subjects was not possible.

From a clinical perspective, our study findings of EIBc should not be considered synonymous with asthma, which is a clinical diagnosis with variable airflow obstruction associated with intermittent and sometimes persistent troublesome symptoms. This study makes no assumptions about the subject's underlying pre-test symptoms, so EIBc should not be conflated with asthma. Likewise, bronchodilator reversibility (improvement in FEV_1 of 12% and 200 mL) is commonly used as an objective test for asthma, but we have not assumed that EIBd also means asthma. Further prospective studies of the sensitivity/specificity of CPET in diagnosing exercise-induced asthma based on EIBc or reversibility based on EIBd are required.

There are limitations to this study. First, this is a single-centre retrospective study of CPET over a 25-year period. Second, we performed incremental cycle ergometry to symptom-limited capacity. Thus, our findings may not be generalisable to other exercises and cycling is thought to induce EIBc with a lower prevalence [49] compared with free running [2], swimming or other sports [50]. Third, we used a threshold of whatever value was at the 5th percentile in the whole study population. In our study this was a 7.6% fall; however, current guidelines recommend demonstrating a fall of 10% post-exercise [7].

All of the current analyses were re-done with a 10% cut-off value as recommended by guidelines and the same findings were found. Higher thresholds (10% fall) increase specificity but at the cost of decreased sensitivity. In both those with EIBc and EIBd, a decreased capacity to exercise was seen with a lower MPO, *i.e.* disability. Surprisingly, any improvement in FEV_1 seen post-exercise was not translated into an increase in capacity to exercise. Fourth, the list of medications subjects were taking prior to exercise was not available in our current database and hence we cannot analyse the potential effects of medications on EIBc or EIBd. This could be done in a prospective manner in a future study. Fifth, our current retrospective database did not record the ethnicity of subjects. The focus of this study was to evaluate sex, lung function and airflow limitation. The Hamilton population is predominantly Caucasian, and correction of predicted reference values for second- and third-generation ethnic immigrants who have lived in Canada their whole life is currently unclear.

Conclusions

EIBc and EIBd occur after exercise, and are influenced by increasing age and lower FEV_1 % pred. Female sex influences EIBc but not EIBd, while airflow limitation influences EIBd but not EIBc.

Author contributions: All authors conceptualised and designed the study, had full access to all the data, and contributed to data analysis, interpretation and writing of the manuscript.

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