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Exercise Induced Bronchoconstriction and Bronchodilation; investigating the effects of age, sex, airflow limitation and the FEV1

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KEY WORDS: respiratory physiology, cardio-pulmonary exercise testing, exercise-induced bronchoconstriction, exercise-induced bronchodilation, smooth muscle, airway nerves

KEY MESSAGE: Exercise induced bronchoconstriction and bronchodilation occurs after exercise and are influenced by increasing age, lower FEV1 % predicted and airflow limitation. Female sex influences EIBc but not EIBd.

ABBREVIATIONS:

AL- Airflow Limitation; BMI- Body Mass Index; CPET- cardiopulmonary exercise test; DLCO- diffusion capacity for carbon monoxide; ECG- electrocardiogram; EIA- exercise induced asthma; EIBc-exercise induced bronchoconstriction; EIBd-exercise induced bronchodilation; ETCO2- End tidal CO2; EVH- eucapnic voluntary hyperapnea; FEV1- Forced Expired Volume over one Second; FIF- Forced Inspiratory Flow; FVC- Forced Vital Capacity; Hb- Haemoglobin; KCO- The carbon monoxide transfer coefficient; Kpm- kilopond meters; MI- Myocardial Infarction; MIP- Maximal Inspiratory Pressure; MEP- Maximal Expiratory Pressure; MPO- maximal power output; PaO2- partial pressure of Oxygen; PECO2- mixed expired CO2; PEFR- Peak Expiratory Flow Rate; PIF- Peak Inspiratory Flow; RQ- Respiratory exchange ratio; RR- Respiratory rate; RV- residual volume; SaO2- Oxygen Saturation; TLC- Total Lung Capacity; VA- Single breath lung volume; VC- Vital Capacity; VO2- oxygen consumption; VCO2- Carbon dioxide production;

ABSTRACT

Exercise induced bronchoconstriction (EIBc) is a recognised response to exercise in asthmatics 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 second (FEV1), airflow limitation (FEV1/FVC<0.7) on the prevalence of EIBc and EIBd. Incremental CPET on cycle ergometry to symptom limitation was performed between 1988-2012 at McMaster University. The FEV1 was performed before and 10 mins after exercise. EIBc was defined as a % fall in FEV1 post exercise below the 5th percentile, whilst EIBd as % increase in FEV1 above the 95% percentile. 35,258 subjects between age 6-95 were included in the study (mean age 53, 60% male, 10.3% had airflow limitation (AL, FEV1/FVC<0.7). The lowest 5% of subjects demonstrated a >7.6% fall in FEV1 post exercise (EIBc), whilst the top 5% a >11% increase (EIBd). The probability of both EIBc and EIBd increased with age and was highest in females across all ages (OR 1.76(1.60-1.94) p<0.0001). The probability of EIBc increased as the FEV1 %predicted declined (<40% OR 4.38(3.04-6.31),p<0.0001), a >2x increased likelihood in females (OR 2.31(1.71-3.113)p<0.0001), with a trend with AL(p=0.06). The probability of EIBd increased as the FEV1 %predicted declined, in the presence of AL (OR 1.55 (1.24-.95) p=0.0001), but sex had no effect. EIBc and EIBd can be demonstrated at the population level and is influenced by age, sex, FEV1 %predicted and airflow limitation.

INTRODUCTION

Physicians, teachers and parents supervising athletic activity in children are often faced with complaints of breathlessness, wheezing, light-headedness and paresthesia 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 ischemia and syncope. Whether such children truly have exercise induced bronchoconstriction or asthma remains a diagnostic challenge without spirometry.

Bronchoconstriction following strenuous muscular activity is common in children and 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 adults. This probably explains why field studies on young children form the bulk of the reported experience in exercise induced asthma (EIA) or exercise induced bronchoconstriction (EIBc). Jones formally described this phenomenon in children in 1962 [2]. However, in 1968, Fitch also noticed severe EIBc in an 18-year-old Olympic Gold Medallist swimmer [3].

Godfrey, Fitch and their colleagues popularized the measurement of spirometry before, during and following exercise. Though less sensitive than other spirometric indices, the forced expired volume over one second (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 asthmatics, 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 Center, spirometry has been measured prior to and 10 minutes after maximum incremental cardiopulmonary exercise tests (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. The FEV_1 was measured before and 10 minutes after incremental exercise to symptom limited capacity in all subjects. The frequency of exercise induced bronchoconstriction (EIBc) and bronchodilation (EIBd) could then be identified in specifically defined subgroups. The contributions of age, sex, baseline FEV1 % predicted, with and without airflow limitation (FEV1/FVC<0.7) on the frequency of EIBc and EIBd were investigated, alone and with interactions.

PROCEDURES AND METHODS

Study Design

This was a retrospective study based on data collected from sequential patients referred for clinical exercise testing at McMaster University Medical Center between 1988-2012. Electronic data download after 2012 was not technically feasible due to a change in the software used. All subjects with pre and post exercise FEV1 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%), dyspnea (12%), pre cardiac rehabilitation (10%), and post myocardial infarction (7%), suspected exercise induced asthma

(3%) and other disorders (congenital heart disease (3%), cystic fibrosis (2%), chronic obstructive pulmonary disease (COPD, 2%).

Study Procedures

Prior to exercise, risks of exercise were explained and informed consent for exercise testing and the use of the data collected for audit and research purposes. The indication for exercise was recorded and the 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 (RV) and total lung capacity (TLC) (MIP & MEP), seated bench press and row, knee extension (quadriceps) and flexion (hamstrings) using maximum contraction against hydraulic resistance with quasi-isokinetic characteristics. Spirometry was measured with a maximum expiratory and inspiratory maneuvers from TLC to RV yielding forced vital capacity (FVC) and forced expired volume over one second (FEV1), peak expiratory flow rates (PEFR), forced expired volume at 25, 50 and 75% of the expired vital capacity. The peak inspirator flow rate and FIF 25, 50 and 75% were also measured. Single breath lung volume (communicating lung volume), diffusion capacity for carbon monoxide (DLCO) and carbon monoxide transfer coefficient (KCO) were measured. Haemoglobin Hb, Hb Co SaO2, and arterialized capillary blood gases were also measured.

CPET involved incremental increases in power on a servo-controlled upright cycle ergometer to symptoms limited capacity. The stepwise increase in power output was 100 kpm (16Watts). During exercise, oxygen uptake, carbon dioxide output, respiratory exchange ratio (RQ),

ventilation, tidal volume, respiratory frequency, heart rate, blood pressure, and electrocardiogram were monitored. After exercise, ECG monitoring continued for 10 minutes, 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, BMI between 20-30, 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: (i) a positive acceleration of FEV1 and maxium power output (MPO) with height; (ii) proportionately higher values in males than females of the same height; (iii) a proportionate decline in FEV1 in both sexes after the age of 35; (iv) and a proportionate increase as age increases to skeletal maturity at age 20. The equation derived is, FEV1 = 0.92*Height (m)2.39 *(1.129 in males) *(1-(0.0076* Age>35)) *(1-(0.012*Age<20)) and MPO=328*Height (m)2.10 * (1.29 in males) *(1-(0.0085*Age>35)) *(1+(0.0034*Age<20))

Study Objectives

Four main questions were investigated: What was the probability of EIBc and EIBd i) at each decade of age in females and males, ii) in those with an exercise capacity achieved of <50%, 50-80% and >80% predicted normal in females and males, iii) in those with an FEV_1 % predicted <50%, 50-80% and >80% with and without airflow limitation (FEV1/VC <70%) and iv) the interaction between sex, airflow limitation ((FEV1/VC <70%) and FEV1% predicted <50%, 50-80% and >80%.

Statistical Analysis

The FEV_1 was expressed as a percentage of the pre-exercise value. No assumption as to normal parametric distribution was assumed. The 5th and 95^{th} percentiles were directly identified. Exercise induced bronchoconstriction (EIBc) was assumed if the FEV_1 post exercise was $<5^{th}$ percentile. Exercise induced bronchodilation (EIBd) was assumed if the FEV_1 post exercise was $>95^{th}$ 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

A total of 35,258 subjects were included between the ages of 6 and 95 (mean age 53, 60% were male, and 10.3% had airflow obstruction (FEV1/FVC<0.7). The distribution of the FEV_1 post exercise expressed as a % of the FEV_1 before exercise is shown in Figure 1. The 5^{th} percentile was 92.4%; the 95^{th} percentile was 111.1%. A total of 1771 subjects were classified as EIBc and 1861 as EIBd. Anthropometrics and baseline respiratory measures are shown in Table 1, and physiological parameters at maximum power output (MPO) are shown in Table 2. Subjects with EIBc and EIBd had a lower FEV1, greater proportion with airflow limitation at baseline, with 34% considered to be normal in both groups (no history of MI, COPD, asthma, normal spirometry and with a normal exercise capacity,).

The effects of sex and ageing

The probability of EIBc and EIBd are shown in Figure 2A and 2B respectively. Females had an increased likelihood of EIBc compared with males (Female OR 1.76 (1.60-1.94; p<0.0001). The probability of EIBc in both males and females was lowest in the 40-50 age group (males 3.2%, females 4.7%) and increased subsequently reaching peak of 10.3% in females and 7.5% in males. Except for those <10 years of age, 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 (OR 1.04 (0.95-1.15; p=0.38). The probability of EIBd in males was lowest in the 10-20 age group (3.2%) and for females in the 30-40 age group (3.2%). For males and females there was a gradual increase in EIBd with age up to of 8.4% in females and 7.5% in males over the age of 80. Importantly, the highest probability of EIBd in females was in those <10 years of age.

The effects of sex and maximum power output

EIBc increased in a positively accelerating manner as the maximum power output (MPO) achieved decreased with females experiencing EIBc to a greater extent than males (Figure 3A, OR for females 1.67 (1.49-1.87) p<0.0001). EIBd also increased substantially as the MPO achieved decreased with females and males but being similarly affected [Figure 3B, OR for female 0.98 (0.8-1.11) p=0.76].

The effects of FEV1% predicted with and without airflow limitation

The probability of EIBc increased as the FEV_1 decreased and was not different in the presence of airflow limitation (Figure 4A, airflow limitation OR 1.06 (0.86-1.30) p=0.59). There was a greater

than 4-fold increased likelihood of EIBc as FEV1 % predicted decreased from >80% to <40% (OR 4.38 (3.04-6.31), p<0.0001).

The probability of EIBd increased as the FEV_1 decreased and was approximately 50% greater in the presence of airflow limitation (Figure 4B, airflow limitation OR 1.51 (1.23-1.86) p<0.0001). The effect of airflow limitation was most noticeable in those with an FEV1>80% and 40-60%.

The effects of sex, airflow limitation and FEV1 % predicted

The probability of EIBc increased in a positively accelerating manner as the FEV1 % predicted declined with a greater than doubling increased likelihood in females (OR 2.31 (1.71-3.113) p<0.0001, Figure 5A,5B). The effect of the presence of airflow limitation did not reach statistical significance (OR 1.34 (0.99-1.81), p=0.06).

The probability of EIBd increased as the FEV1 % predicted declined with no effects of sex (Female OR 1.12 (0.90-1.40) p=0.32). The presence of airflow limitation increased the probability of EIBd (OR 1.55 (1.24-.95) p=0.0001).

DISCUSSION

This is the largest study to date to describe exercise induced bronchoconstriction and bronchodilation after cardio-pulmonary exercise testing 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 or more in FEV1 post exercise (EIBc), whilst the top 5% (1865) demonstrated a greater than 11% increase (EIBd). The main finding was that the probability of EIBc increased with increasing age, female sex, and lower maximum power output (MPO) % predicted, and lower FEV1 % predicted pre-exercise. The probability of EIBd also increased with increasing age, lower MPO % predicted and FEV1% predicted, 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 leukotrienes released into the airways [8–13]. However, alternative explanations include hypersensitivity of sensory nerves, autonomic imbalance[14] between the beta-2 adrenoceptors and m3 muscarinic receptors and airway epithelial shedding and damage [15–17]. Firstly, 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). Secondly, all subjects performed CPET in the same room, under the same temperature (24 deg) and humidity (45% relative humidity), hence, these were constant for all subjects. In

asthmatics, an important component of airways 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 the airway reactivity [18]. Unfortunately, we do not have data on methacholine airway hyper-reactivity in these subjects. Third, we are not aware of sex differences in beta-2, M3 muscarinic activity, and mast cell function in humans. Sex difference in peripheral vascular adrenergic receptors have been reported [19]. Estradiol, progesterone and testosterone receptors have been found to be expressed on mast cells in animal models and human tissue but no evidence of differential effects to stimulation based on sex[20–23]. Androgens modulate Th2 inflammation in murine asthma models [24], by attenuating ILC2[25], and downstream IL-5[26] and IL-17 [27] .

But 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 >50 (Figure 2A). This suggests loss of oestrogen after menopause or the presence of androgens in males might be implicated. 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 is greatest in female asthmatics [31]. Furthermore, bronchoconstriction further sensitises airway nerves [32]. Leukotriene D4[33], neurokinins[34], prostaglandin D2[35] release have all been implicated in animal models .This may also explain why a lower FEV1 % predicted may increase the likelihood of EIBc. It must be noted that the increased respiratory drive during exercise is likely to also activity rapidly activating receptors (RARs) rather than just the chemically

sensitivity c-fibres. Exactly how and why exercise would sensitise c-fibres and/or RARs more in females compared with males, and subsequently resulting in an increased parasympathetic activity and bronchoconstriction needs further evaluation.

The sex differences that we have shown over the age ranges and at different degrees of FEV1 % predicted, 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 sports such as swimmers and cold air athletes the range is considerably large between 25-75% [37–40]. A recent systematic review of 60 studies evaluating EIBc found an overall prevalence of 23% of EIBc in athletes[41]. But 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 FEV1 in our study with increasing age, worsening FEV1% predicted and the presence of airflow limitation. EIBd has previous been studied in small numbers of subjects. In 1959, Capel and Smart showed a 24% increase (3%-52%) in FEV_1 during exercise in patients with obstructive lung disease. The FEV_1 returned to baseline 5 minutes after exercise cessation[42]. Gelb et. Al reported a 20 % increase in FEV_1 during exercise in seven asthmatic men, and proposed that stretching of the airway wall during exercise releases the products of cyclooxygenase play a role in EIBd [43]. Deep inspiration is also known to be bronchoprotective[44], and with exercise as the ventilation and lung volumes increase, 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 increases with increasing power. In recovery, these effects recede. In this context, EIBc may be due to an increased cholinergic activity or beta-2 receptor desensitisation by the excessive adrenergic activity during exercise. This mechanism though postulated with excessive beta-2 agonist use [48], has not been investigated in the context of exercise. In contrast, in EIBd there is persistence of adrenergic and anti-cholinergic activity and this might be predcited in those subjects whose heart rate remains high. However, though heart rate was recorded, it 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 their underlying pre-test symptoms so EIBc should not be conflated with asthma. Likewise, bronchodilator reversibility (improvement in FEV1 of 12% and 200ml) is commonly used an objective test for asthma but 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. Firstly, this is a single center retrospective study of CPET over a 25-year period. Secondly, we performed incremental cycle ergometry to symptom limited capacity. Thus, our findings may not be generalizable with other exercises and cycling is thought to induce EIBc with a lower prevalence[50] compared with free running[2], swimming, or other sports [51]. Third, we used a threshold of whatever value was at the 5 percentile in the whole study population. In our study this was 7.6% fall, however, current guidelines recommend demonstrated 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 FEV1 seen post exercise was not translated into an increase in the capacity to exercise. Fourth, we do not have available the list of medications subjects were taking prior to exercise in our current database and hence 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 handling of 2^{nd} and 3^{rd} generation ethnic immigrants who have lived in Canada their whole life can be challenging.

CONCLUSIONS

Exercise induced bronchoconstriction and bronchodilation occurs after exercise and are influenced by increasing age and lower FEV1 % predicted. Female sex influences EIBc but not EIBd, whilst airflow limitation influences EIBd, but not EIBc.

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TABLE 1: Demographics and Baseline Physiology. Mean and 95% Confidence Intervals shown. P-value calculated using ANOVA. BMI; body mass index, FEV1; forced expiratory volume in 1 second, FVC; forced vital capacity, DLCO; diffusion lung capacity of carbon monoxide, VA; alveolar volume, KCO; transfer co-efficient for carbon monoxide, MIPS; maximum inspiratory pressure strength, MEPS; maximum expiratory pressure strength

VARIABLE	NEITHER EIBc OR EIBd			*Exercise Induced* Bronchoconstriction (EIBc)			Exercise Induced Bronchodilation (EIBd)			p-value
	Mean	-95% C.I.	+95% C.I.	Mean	-95%C.I.	+95% C.I.	Mean	-95%C.I.	+95% C.I.	
Age	**52.7**	52.47	52.86	**54.4**	53.56	55.33	**55.9**	55.11	56.69	<0.0001
Male (%)	**60.7**	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	**27.4**	27.35	27.47	**27.3**	27.00	27.54	**27.5**	27.24	27.75	0.4441
FEV1 (l)	**2.79**	2.78	2.80	**2.33**	2.29	2.37	**2.30**	2.26	2.34	<0.0001
FEV1%	**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

FEV1/FVC (%)	**80.07**	79.97	80.16	**77.66**	77.14	78.18	**75.78**	75.24	76.33	<0.0001
FEV1/FVC <0.7 (%)	**0.09**	0.09	0.09	**0.18**	0.16	0.20	**0.22**	0.20	0.24	<0.0001
DLCO (ml/mmHg/min)	**22.50**	22.43	22.57	**20.17**	19.85	20.50	**21.14**	20.83	21.45	<0.0001
VA (l)	**5.20**	5.18	5.21	**4.60**	4.54	4.66	**4.96**	4.90	5.02	<0.0001
KCO (ml/mmHg/min/l)	**4.39**	4.38	4.40	**4.44**	4.39	4.49	**4.35**	4.30	4.40	0.0317
Quad Strength (kg)	39.79	38.83	40.76	42.29	41.37	43.20	46.84	46.62	47.07	<0.0001
MIPS (cm H20)	65.73	64.32	67.14	68.83	67.48	70.19	75.46	75.13	75.80	<0.0001
MEPS (cm H20)	97.30	95.44	99.16	99.41	97.71	101.11	107.37	106.95	107.79	<0.0001

TABLE 2: Physiological Assessment at Peak Exercise During Incremental Cardio-Pulmonary Exercise Testing. RR; respiratory rate, MPO; maximum power output, VO2; oxygen consumption, VCO2; carbon dioxide production, RQ; respiratory quotient, SaO2; saturation of oxygen, PaO2;partial pressure of arterial oxygen, PETCO2; partial pressure of end-tidal carbon dioxide.

VARIABLE	NEITHER EIBc OR EIBd			Exercise Induced Bronchoconstriction (EIBc)			Exercise Induced Bronchodilation (EIBd)			p-value
	Mean	-95% C.I.	+95% C.I.	Mean	-95% C.I.	+95% C.I.	Mean	-95% C.I.	+95% C.I.	
VALUES AT MAXIMUM EXERCISE										
Ventilation (l/min)	**58.34**	58.08	**58.59**	**50.44**	49.42	51.46	**51.76**	50.76	52.77	<0.0001
RR (breaths/min)	**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)	**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
VO2 l/min	**1.65**	1.64	1.65	**1.42**	1.38	1.45	**1.45**	1.42	1.48	<0.0001
VCO2 l/min	**1.79**	1.78	1.80	**1.50**	1.47	1.54	**1.56**	1.53	1.60	<0.0001
RQ	**1.08**	1.08	1.08	**1.05**	1.05	1.06	**1.07**	1.06	1.07	<0.0001
SaO2 %	**95.61**	95.58	95.64	**95.13**	94.99	95.27	**95.14**	95.01	95.28	<0.0001
PaO2 mmHg	**85.24**	85.00	85.49	**82.71**	81.67	83.75	**82.70**	81.71	83.69	<0.0001

PETCO2 mmHg	**35.98**	35.92	36.04	**35.80**	35.57	36.03	**35.96**	35.68	36.23	0.377

FIGURES

FIGURE 1: Distribution of changes in FEV1 post-exercise as a % of pre-exercise

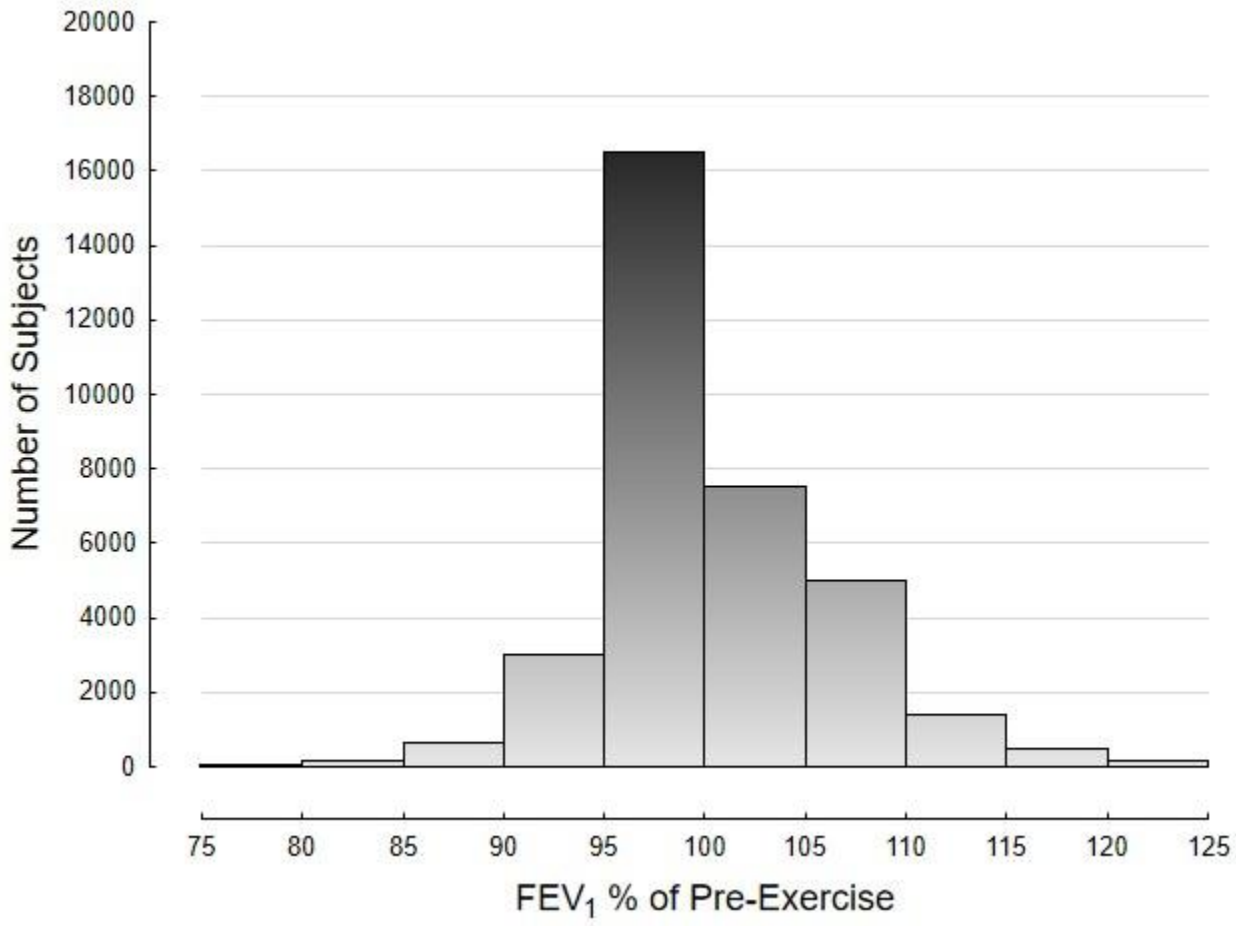

FIGURE 2: The probability of exercise induced bronchoconstriction and bronchodilation based on age and sex. Mean and 95% confidence intervals shown.

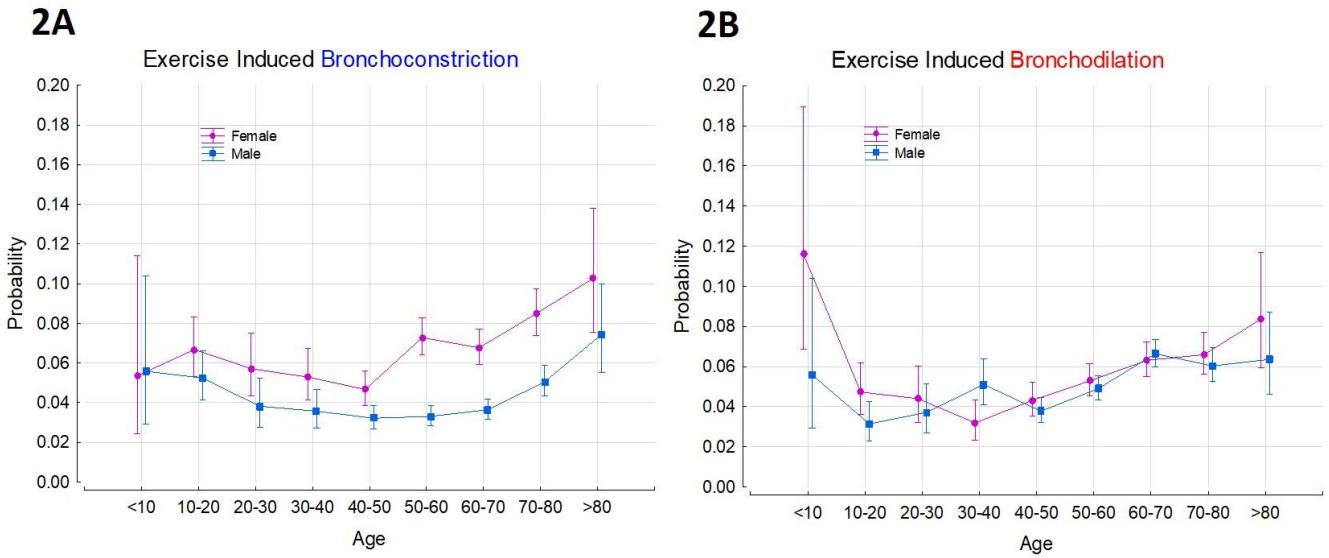

FIGURE 3: The probability of exercise induced bronchoconstriction and bronchodilation based on maximum power output (MPO) and sex. Mean and 95% confidence intervals shown.

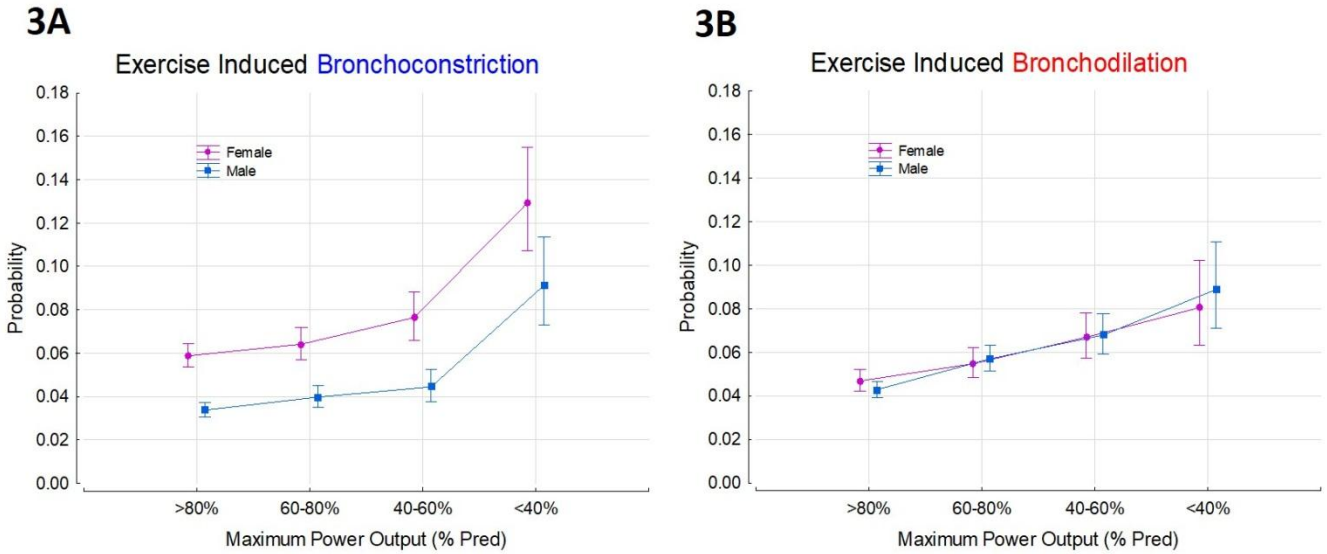

FIGURE 4: The probability of exercise induced bronchoconstriction and bronchodilation based on FEV1 % predicted and the presence of absence of airflow limitation (FEV1/FVC<0.7). Mean and 95% confidence intervals shown.

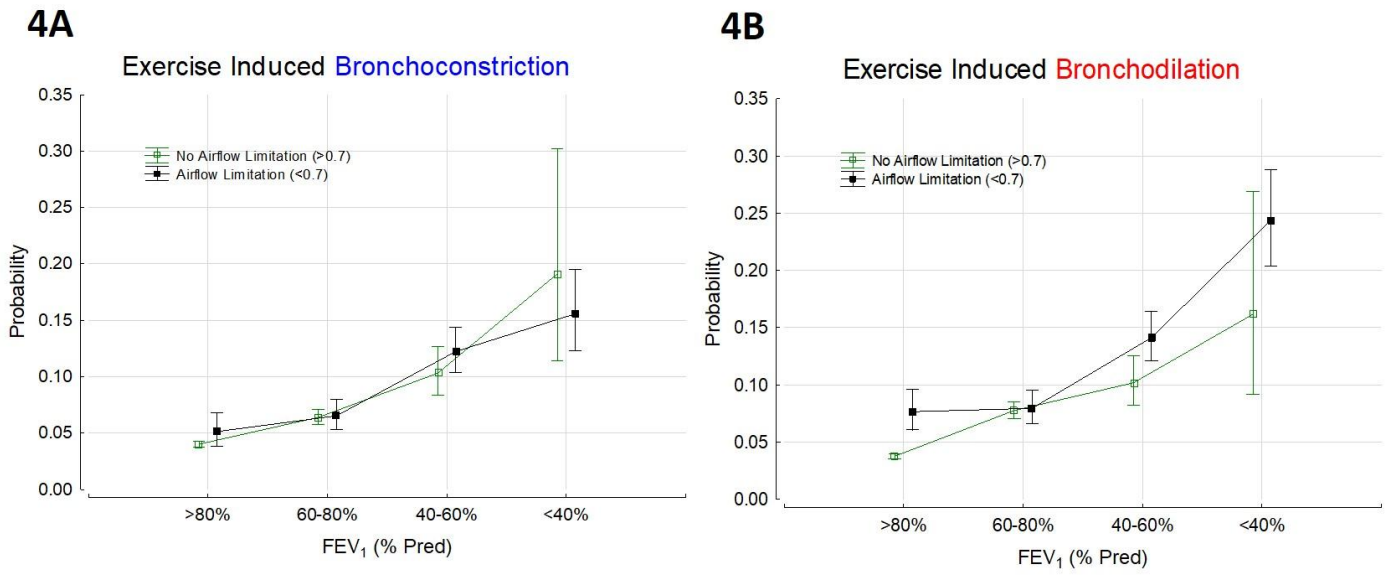

FIGURE 5: The probability of exercise induced bronchoconstriction and bronchodilation based on sex, FEV1% predicted and airflow limitation (FEV1/FVC<0.7). Mean and 95% confidence intervals shown.