Supplement: Reduced tidal volume inflection point and elevated operating lung volumes in well-controlled females with asthma

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Running title: Supplement: V_T-inflection and dyspnea in females with asthma

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Supplement: V_T-inflection and dyspnea in females with asthma

Results

Male participant characteristics can be found in Supplementary Table 1. Pulmonary function pre-bronchodilator, post-bronchodilator, and following cardiopulmonary exercise test (CPET) can be found in Supplementary Table 2. Males with and without asthma had a significant increase in forced expired volume in 1 second following CPET due to exercise induced bronchodilation (1).

Ventilatory and metabolic responses to exercise

Male metabolic and ventilatory responses at highest equivalent workload (150W), the tidal volume (V_T)-inflection point, and peak exercise can be found in Supplementary Table 3. Ventilation during submaximal exercise was not significantly different between males with asthma and male controls (p=0.56) as both breathing frequency and V_T were not significantly different between the two groups (p=0.07 and p=0.16, respectively) (Supplementary Figure 1A and 1B).

When V_T-inflection is expressed as a percent of $\dot{V}O_{2peak}$, there was no significant difference between female controls and females with asthma (Control: 81 ± 9% vs. Asthma: 77 ± 10%; p= 0.155). However, a post-hoc analysis of the data suggests the current study was underpowered to find significance (β=0.42) and future exploration could be beneficial.

Females with asthma did not demonstrate ventilatory efficiency impairments as compared with female controls as $\dot{V}_E/\dot{V}CO_2$ at peak exercise and the lowest 30-seconds (Nadir) were not significantly different between females with asthma and controls (p=0.595 and p=0.312, respectively). Further, the $\dot{V}_E/\dot{V}CO_{2slope}$ was not significantly different between conditions (p=0.708), and the y-intercept showed no significant group differences (p=0.934). Lastly, end-tidal PCO_2 at peak exercise was not different between females with asthma and controls (p=0.336).

Brotto AR, *et al. BMJ Open Respir Res* 2023; 10:e001791. doi: 10.1136/bmjresp-2023-001791

Supplement: V_T-inflection and dyspnea in females with asthma

Similar to females with asthma, $\dot{V}_E/\dot{V}CO_2$ in males with asthma were not different between groups at peak exercise (p=0.29) or the lowest 30-seconds (Nadir) (p=0.23). Further, $\dot{V}_E/\dot{V}CO_{2slope}$ was not significantly different between males with asthma and male controls (Control: 23.1 ± 2.7 vs. Asthma: 22.4 ± 3.0; p=0.48). End-tidal PCO_2 at peak exercise was also not different between the two groups (p=0.61).

Perceptual responses to exercise

The dyspnea-ventilation slope was not significantly different between females with asthma and female controls (Control: 0.07 ± 0.03 vs. Asthma: 0.08 ± 0.02; p=0.13) (Figure 2C). Similarly, the dyspnea-ventilation slope was not different between males with asthma and male controls (Control: 0.06 ± 0.02 vs. Asthma: 0.06 ± 0.01; p=0.46) (Supplementary Figure 2C).

In females with asthma, 13 participants terminated the test due to “leg discomfort”, while 3 participants terminated the test due to “both leg and breathing discomfort”. In comparison, 14 female control participants terminated the test due to “leg discomfort” and 2 participants terminated the test due to “both leg and breathing discomfort”. The selection frequency of the reason for termination was not significantly different (p=0.50). In males with asthma, 12 participants terminated the test due to “leg discomfort”, while 4 participants terminated the test due to “breathing discomfort”. In comparison, 13 male control participants terminated the test due to “leg discomfort” and 3 participants terminated the test due to “both leg and breathing discomfort”. The selection frequency of the reason for termination was significantly different (p=0.02).

Supplement: V_T-inflection and dyspnea in females with asthma

1. Rossman MJ, Petrics G, Klansky A, Craig K, Irvin CG, Haverkamp HC. Exercise-induced Bronchodilation Equalizes Exercise Ventilatory Mechanics despite Variable Baseline Airway Function in Asthma. Med Sci Sports Exerc. 2022;54(2):258-66. doi: 10.1249/MSS.0000000000002793. PubMed PMID: 34559730.

Supplement: V_T-inflection and dyspnea in females with asthma

Figure Captions

Supplementary Figure 1. Ventilatory and lung mechanic responses to exercise in males with asthma and male controls. This graph shows data means ± standard deviation. *Signifies $p<0.05$ between male controls and males with asthma.

Supplementary Figure 2. Dyspnea response to exercise in males with asthma and male controls. This graph shows data means ± standard deviation. *Signifies $p<0.05$ between male controls and males with asthma.

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Supplement: V_T-inflection and dyspnea in females with asthma

Supplementary Table 1. Male participant characteristics

Variable	Control	Asthma	p-value
n	16	16	
Age (years)	24 ± 3	24 ± 5	0.77
Height (m)	1.78 ± 0.05	1.78 ± 0.08	0.32
Weight (kg)	79.5 ± 14.0	77.8 ± 11.9	0.26
BMI ($kg \cdot m^{-2}$)	24.9 ± 3.1	24.5 ± 3.0	0.44
ACQ Score	0.0 ± 0.0	0.7 ± 0.8	**0.01**
Allergies (%)	20	63	
Medications			
SABA (%)	0	50	
ICS (%)	0	31	
Combination (%)	0	13	
Airway Evaluation			
Positive Reversibility	0/16	10/16	
Mean FEV_1 Change (%)	6 ± 3	10 ± 5	**0.02**
Positive MCT (%)	0/16	6/16	
Mean FEV_1 Change (%)	3 ± 2	14 ± 8	**0.00**
Positive ECT (%)	0/16	1/16	
Mean FEV_1 Change (%)	2 ± 1	4 ± 4	0.18

Values are expressed as mean ± SD. BMI: body mass index; ACQ: asthma control questionnaire; SABA: short-acting beta agonist; ICS: inhaled corticosteroid; MCT: methacholine challenge test; ECT: exercise challenge test; FEV_1: forced expired volume in 1-second. Note: positive reversibility defined as a change in FEV_1 by 12% following bronchodilator

66

Supplement: V_T-inflection and dyspnea in females with asthma

Supplementary Table 2. Pulmonary function with and without bronchodilator and following exercise in male control and asthma

	Control			Asthma		
	Pre-BD	Post-BD	Post-CPET	Pre-BD	Post-BD	Post-CPET
Spirometry						
FVC (L)	6.06 ± 1.03	6.16 ± 0.99	6.31 ± 1.15	5.62 ± 0.86	5.65 ± 0.92	5.53 ± 0.70
FVC (% predicted)	107 ± 12	109 ± 11	110 ± 17	105 ± 15	107 ± 16	107 ± 16
FEV_1 (L)	4.83 ± 0.72	5.10 ± 0.74$^{\$}$	5.20 ± 0.56$^{\$}$	4.03 ± 0.62*	4.41 ± 0.67$^{\$}$	4.15 ± 0.71$^{\$}$
FEV_1 (% predicted)	101 ± 13	108 ± 9$^{\$}$	109 ± 10$^{\$}$	90 ± 18*	99 ± 17$^{\$}$	96 ± 17$^{\$}$
FEV_1/FVC	80 ± 4	83 ± 4$^{\$}$	84 ± 9$^{\$}$	72 ± 9*	79 ± 9$^{\$}$	75 ± 9$^{\$}$
FEV_1/FVC (% predicted)	95 ± 5	99 ± 5$^{\$}$	99 ± 11$^{\$}$	85 ± 9*	92 ± 9$^{\$}$	89 ± 10$^{\$}$
Lung Volumes						
TLC (L)	7.69 ± 1.14			7.76 ± 1.33		
TLC (% predicted)	107 ± 15			113 ± 21		
RV (L)	1.32 ± 0.50			1.43 ± 0.28		
RV (% predicted)	86 ± 32			95 ± 15		
IC (L)	3.88 ± 0.74			3.57 ± 0.67		
IC (% predicted)	104 ± 16			100 ± 16		
Diffusion Capacity						
DLCO ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	37.6 ± 4.2			35.3 ± 5.7		
DLCO (% predicted)	110 ± 10			107 ± 11		

Values expressed as mean ± standard deviation. FVC: forced vital capacity; FEV_1: forced expired volume in 1 second; TLC: total lung capacity; RV: reserve volume; IC: inspiratory capacity; DLCO: diffusing capacity of carbon monoxide; BD: bronchodilator; CPET: cardiopulmonary exercise test. *Signifies $p<0.05$ as compared to controls. $^{\$}$Signifies $p<0.05$ as compared to Pre-BD.

Supplement: V_T-inflection and dyspnea in females with asthma

Supplementary Table 3. Metabolic and ventilatory responses in males at 150W, tidal volume inflection point, and peak exercise.

	150 Watts		V_T-Inflection Point		Peak	
	Control	Asthma	Control	Asthma	Control	Asthma
$\dot{V}O_{2peak}$ (L/min)	2.20 ± 0.24	2.28 ± 0.25	3.21 ± 0.69	3.07 ± 0.72	3.90 ± 0.68	3.78 ± 0.60
$\dot{V}O_{2peak}$ (ml/kg/min)	26.8 ± 3.0	29.8 ± 4.4	38.9 ± 7.0	40.0 ± 7.6	47.4 ± 7.0	49.0 ± 8.4
$\dot{V}O_{2peak}$ (% predicted)	---	---	---	---	134 ± 19	133 ± 19
$\dot{V}_E$ (L/min)	56.2 ± 9.6	62.4 ± 10.4	93.7 ± 25.3	91.4 ± 27.8	139.6 ± 26.6	141.7 ± 32.4
Power Output (W)	150 ± 0	150 ± 0	220 ± 44	206 ± 47	278 ± 43	258 ± 50
RER	1.01 ± 0.08	1.04 ± 0.07	1.09 ± 0.06	1.08 ± 0.08	1.17 ± 0.06	1.15 ± 0.07
$\dot{V}_E/\dot{V}CO_2$	25 ± 2	26 ± 2	27 ± 3	27 ± 3	32 ± 4	33 ± 4
$\dot{V}CO_2$ (L/min)	2.21 ± 0.23	2.38 ± 0.28	3.50 ± 0.73	3.33 ± 0.86	4.40 ± 0.64	4.25 ± 0.71
$P_{ET}CO_2$ (mmHg)	42.6 ± 3.1	40.8 ± 3.3	40.5 ± 4.2	39.4 ± 4.3	34.6 ± 3.5	33.8 ± 4.6
fb (breaths/min)	24 ± 5	29 ± 7	31 ± 6	34 ± 8	46 ± 9	52 ± 11
V_T (L)	2.44 ± 0.43	2.30 ± 0.36	3.05 ± 0.58	2.78 ± 0.65	3.10 ± 0.51	2.74 ± 0.43*
IC (L)	3.82 ± 0.77	3.61 ± 0.54	3.95 ± 0.73	3.68 ± 0.63	3.89 ± 0.41	3.46 ± 0.47*
IC (%TLC)	49 ± 5	47 ± 6	51 ± 5	49 ± 7	51 ± 6	45 ± 6
EELV (%TLC)	51 ± 5	53 ± 6	49 ± 5	51 ± 7	49 ± 6	55 ± 6
IRV (%TLC)	16 ± 4	17 ± 4	11 ± 5	12 ± 4	11 ± 6	9 ± 5
V_T/IC (%)	67 ± 8	64 ± 8	78 ± 10	76 ± 12	80 ± 11	80 ± 10
EILV (%TLC)/ $\dot{V}_E$	1.55 ± 0.32	1.36 ± 0.20	1.04 ± 0.28	1.06 ± 0.33	0.67 ± 0.11	0.73 ± 0.16
EFL (%)	0 ± 0	13 ± 28*	10 ± 23	23 ± 28	28 ± 27	54 ± 28*
HR (beats/min)	137 ± 13	145 ± 14	167 ± 14	165 ± 22	186 ± 7	181 ± 15
SpO_2 (%)	95 ± 4	96 ± 4	95 ± 2	95 ± 4	94 ± 4	96 ± 2
Dyspnea	2.1 ± 1.3	2.9 ± 1.1	4.1 ± 1.6	4.8 ± 1.5	7.1 ± 1.8	7.7 ± 1.5
Leg Discomfort	3.3 ± 1.4	3.8 ± 1.1	5.9 ± 2.1	5.9 ± 1.6	9.0 ± 1.3	9.1 ± 1.2

Values are expressed as mean ± standard deviation. $\dot{V}O_2$: rate of oxygen consumption; $\dot{V}E$: minute ventilation; RER: respiratory exchange ratio; $\dot{V}CO_2$: rate of carbon dioxide production; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide; fb: breathing frequency; V_T: tidal volume; IC: inspiratory capacity; EELV: end-expiratory lung volume; EILV: end-inspiratory lung volume; IRV: inspiratory reserve volume; EFL: expiratory flow limitation; HR: heart rate; SpO_2: arterial oxygen saturation. *Signifies $p<0.05$ between asthma and control.

69

Supplement: V_T-inflection and dyspnea in females with asthma

Supplementary Table 4. Metabolic and ventilatory responses in females at 125W, tidal volume inflection point, and peak exercise.

	125 Watts		V_T-inflection Point		Peak	
	Control	Asthma	Control	Asthma	Control	Asthma
$\dot{V}O_{2peak}$ (L/min)	1.71 ± 0.12	1.84 ± 0.19	2.19 ± 0.42	1.85 ± 0.35*	2.70 ± 0.29	2.40 ± 0.35*
$\dot{V}O_{2peak}$ (ml/kg/min)	27.9 ± 3.3	30.6 ± 5.6	35.7 ± 6.7	30.6 ± 6.2*	44.0 ± 5.3	39.8 ± 7.1
$\dot{V}O_{2peak}$ (% predicted)	---	---	---	---	156 ± 18	139 ± 20*
$\dot{V}_E$ (L/min)	48.9 ± 6.3	56.6 ± 8.6*	70.2 ± 16.5	57.7 ± 12.3*	110.1 ± 14.2	91.6 ± 15.7*
Power Output (W)	125 ± 0	125 ± 0	163 ± 33	128 ± 26*	216 ± 22	177 ± 25*
RER	1.03 ± 0.07	1.07 ± 0.07	1.11 ± 0.07	1.07 ± 0.06	1.21 ± 0.05	1.17 ± 0.08
$\dot{V}_E/\dot{V}CO_2$	28 ± 2	29 ± 3	28.8 ± 2.0	29.2 ± 2.1	34 ± 3	33 ± 3
$\dot{V}CO_2$ (L/min)	1.75 ± 0.17	1.95 ± 0.17*	2.43 ± 0.50	1.98 ± 0.41*	3.25 ± 0.26	2.77 ± 0.38*
$P_{ET}CO_2$ (mmHg)	38.7 ± 2.6	37.0 ± 3.3	37.1 ± 2.6	36.9 ± 2.5	31.9 ± 2.5	32.7 ± 2.4
fb (breaths/min)	27 ± 4	33 ± 7*	32 ± 6	32 ± 6	49 ± 7	46 ± 8
V_T (L)	1.87 ± 0.25	1.76 ± 0.21	2.21 ± 0.39	1.82 ± 0.31*	2.27 ± 0.32	2.01 ± 0.20*
IC (L)	2.87 ± 0.42	2.54 ± 0.30*	2.90 ± 0.42	2.57 ± 0.25*	2.87 ± 0.40	2.51 ± 0.31*
IC (%TLC)	53 ± 7	51 ± 5	52 ± 7	51 ± 7	53 ± 7	51 ± 6
EELV (%TLC)	47 ± 7	49 ± 5	48 ± 7	49 ± 7	47 ± 7	50 ± 7
IRV (%TLC)	18 ± 5	15 ± 5*	12 ± 6	15 ± 4	11 ± 5	10 ± 4
Vt/IC (%)	66 ± 7	71 ± 10	77 ± 10	71 ± 8	80 ± 8	79 ± 7
EILV (%TLC)/ $\dot{V}_E$	1.70 ± 0.24	1.56 ± 0.24	1.34 ± 0.36	1.53 ± 0.30	0.83 ± 0.11	1.01 ± 0.17*
EFL (%)	0 ± 0	14 ± 27*	3 ± 10	28 ± 21*	16 ± 25	39 ± 33*
HR (beats/min)	151 ± 15	162 ± 14*	169 ± 15	162 ± 17	185 ± 10	182 ± 12
SpO_2 (%)	96 ± 2	97 ± 2	97 ± 3	97 ± 2	96 ± 4	96 ± 2
Dyspnea	2.1 ± 1.2	3.4 ± 1.0*	3.5 ± 1.8	3.8 ± 1.2	7.1 ± 2.0	7.4 ± 2.3
Leg Discomfort	2.9 ± 0.8	4.6 ± 1.2*	4.5 ± 1.7	4.9 ± 1.9	8.7 ± 1.7	9.1 ± 1.0

Values are expressed as mean ± standard deviation. $\dot{V}O_2$: rate of oxygen consumption; $\dot{V}E$: minute ventilation; RER: respiratory exchange ratio; $\dot{V}CO_2$: rate of carbon dioxide production; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide; fb: breathing frequency; V_T: tidal volume; IC: inspiratory capacity; EELV: end-expiratory lung volume; EILV: end-inspiratory lung volume; IRV: inspiratory reserve volume; EFL: expiratory flow limitation; HR: heart rate; SpO_2: arterial oxygen saturation. *Signifies $p<0.05$ between asthma and control.