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Combined effects of mild-to-moderate obesity and asthma on physiological and sensory responses to exercise

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ABSTRACT

Despite the close link between asthma and obesity, there are no studies that have evaluated the sensory and physiological responses to exercise in obese asthmatics. We recently demonstrated that normal weight asthmatics with well controlled disease have preserved cardiorespiratory and sensory responses to exercise relative to non-asthmatic controls. However, these similarities may not hold true in patients with combined obesity and asthma. Accordingly, we sought to determine if combined asthma and obesity was associated with deleterious effects on cardiorespiratory fitness, exercise performance, dyspnoea, and physiological responses to exercise. Fourteen well-controlled obese asthmatics and fourteen age-matched normal weight asthmatics performed routine spirometry and underwent an incremental cardiopulmonary cycle test to assess the ventilatory, pulmonary gas exchange, cardiovascular, and sensory responses to exercise. Groups were well matched for age, height, spirometry, and asthma control. Obese asthmatics had a significantly greater body mass index (33 ± 3 vs. 23 ± 1 kg/m^2, $p < 0.001$) and lower self-reported activity levels by 47 % relative to normal weight asthmatics ($p < 0.05$). Obese asthmatics had a significantly lower maximal oxygen uptake (VO_2) (82 ± 14 vs. 92 ± 10 %predicted) and work rate (75 ± 8 vs. 89 ± 13 %predicted) relative to normal weight asthmatics ($p < 0.05$). The anaerobic threshold occurred at a lower VO_2 in obese asthmatics vs. normal weight asthmatics (54 ± 15 vs. 66 ± 16 %predicted, $p < 0.05$). Ventilatory responses were superimposed throughout exercise with no evidence of a ventilatory limitation in either group. Cardiovascular responses were normal in both groups. Dyspnoea responses were similar but the obese asthmatics experienced greater leg fatigue ratings at submaximal work rates. In conclusion, obese individuals with well controlled asthma have reduced cardiorespiratory fitness and greater leg fatigue ratings relative to normal weight asthmatics. The relatively reduced cardiorespiratory fitness and exercise performance in obese compared to normal weight asthmatics is most likely driven by their more sedentary lifestyle and resultant deconditioning rather than due to respiratory factors.

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1. Introduction

The prevalence of obesity is rising at an alarming rate throughout the world, particularly in developing countries. Obesity is an established risk factor for cardiovascular disease, diabetes mellitus, certain cancers, and osteoarthritis among other conditions [1,2]. There is also a growing body of epidemiological data linking obesity and asthma [3–5]. Indeed, the vast majority of studies demonstrate an increased prevalence of asthma in overweight and obese individuals across multiple age groups and ethnicities [6–10]. Longitudinal data provides compelling evidence that obesity precedes asthma and that the relative risk of incident asthma increases with increasing body mass index (BMI) [11–13]. The link between asthma and obesity is reinforced by studies showing improvements in airway function, dyspnoea, use of rescue

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medications, and hospitalizations in asthmatics following surgical or diet-induced weight loss [14–17].

Obesity is associated with a number of physiological changes that may influence the cardiopulmonary and sensory responses to exercise. For example, obese individuals tend to adopt a more rapid and shallow breathing pattern relative to normal weight individuals [18,19]. Ofir et al. [19] found that obese women had higher metabolic and ventilatory requirements and greater dyspnoea and expiratory flow limitation during exercise compared to non-obese women. It stands to reason that the aforementioned ventilatory and sensory changes associated with obesity would be amplified in those with co-existing pulmonary conditions. Despite the close link between asthma and obesity, there are no studies that have evaluated the sensory and physiological responses to exercise in individuals with mild-to-moderate obesity and well controlled asthma. We recently demonstrated that normal weight asthmatics with well controlled disease have preserved cardiorespiratory and sensory responses to exercise relative to non-asthmatic controls [20]. However, these similarities may not hold true in patients with combined obesity and asthma. Therefore, we sought to determine if obese asthmatics have diminished aerobic fitness and altered cardiorespiratory and sensory responses to exercise relative to normal weight asthmatics. We hypothesized that obese asthmatics would have a reduced aerobic capacity, increased ventilatory limitations, and increases in dyspnoea and leg fatigue ratings relative to normal weight asthmatics.

2. Methods

2.1. Participants

Fourteen obese asthmatics (BMI $\geq$ 30 kg/m^2) were recruited from the Asthma Clinic at the National Institute of Respiratory Diseases in Mexico City. For comparison purposes, we also included data from fourteen normal weight asthmatics that participated in a previously published study [20]. The diagnosis of Asthma in both groups was determined using established criteria [21]. All asthmatics had to meet one of the following criteria: history of positive reversibility of 200 ml and 12% in forced vital capacity (FVC) or forced expiratory volume in 1 s (FEV_1) [22] and/or history of exercise induced bronchoconstriction [23]. Subjects in this study were also required to meet the criteria for well controlled asthma according to the Global Initiative for Asthma (GINA) Guidelines and the Asthma Control Test [24]. Participants were excluded if they had an acute exacerbation or were on oral corticosteroids, statins or beta blockers within 4 weeks of enrollment; had any disease that could limit or interfere with exercise testing; and if they were regularly participating in moderate or vigorous physical activity.

2.2. Experimental overview

The experimental protocol was based upon a similarly designed study in normal weight asthmatics [20]. The present study was approved by the National Institute of Respiratory Diseases Research Ethics Board (C15-11) and written informed consent was obtained from all participants. Participants were asked to refrain from their respiratory medications for 24 h; and caffeine, heavy meals and alcohol for at least 12 h prior to testing. On day 1, participants were screened for eligibility prior to the completion of medical history and physical activity (International Physical Activity Questionnaire – Short Form (IPAQ-SF)) questionnaires, anthropometric measurements, and pre- and post-bronchodilator spirometry. On day 2, subjects were instrumented with an arterial catheter followed by a symptom limited incremental cardiopulmonary exercise test.

2.3. Pulmonary function

Pre- and post-bronchodilator (400 μg salbutamol) spirometry was performed (Sensormedics Vmax 229, Yorba Linda, CA) according to recommended guidelines [25] and values were expressed as %predicted [26]. Spirometry and maximum voluntary ventilation (MVV) were performed prior to the exercise test by all participants on day 2.

2.4. Cardiopulmonary exercise testing

Exercise testing was performed using an electronically-braked cycle ergometer (Ergoselect 100, Ergoline, Germany) and a breath-by-breath cardiopulmonary testing system (Jaeger Oxycon-Pro, VIASYS Healthcare, Germany) with simultaneous measurement of electrocardiography. Details of the incremental exercise protocol have been described elsewhere [20]. The modified 10-point Borg scale was used to measure "breathing discomfort" and "leg fatigue" during exercise. The anaerobic threshold was determined using the V-slope method [27]. Predicted work rate values came from Jones [28], predicted VO_2 from Wasserman [29], and predicted heart rate was calculated as 210 − (age × 0.65).

2.5. Pulmonary gas exchange

Arterial catheterization of the radial artery was performed under local anesthesia (2% lidocaine). Arterial blood-gases were measured at moderate altitude (~2,240 m, barometric pressure = 585 mmHg, inspired PO_2 = 113 mmHg). Arterial blood-gases were measured after ~15 min of quiet breathing, with the subjects sitting upright, and at maximal exercise. Prior to each blood-gas sample, 5 ml of blood was withdrawn and discarded to eliminate dead space. Samples of 3 ml were then collected in pre-heparinized syringes. Air bubbles were immediately evacuated and the samples were analyzed within 30 s using a calibrated gas analyzer (ABL800 FLEX, Radiometer, Copenhagen, Denmark). Arterial oxygen saturation (%SaO_2) was measured using co-oximetry (i.e., multi-wavelength spectrophotometry). Arterial blood gases were corrected for axillary temperature (Suretemp® Plus 692, Welch Allyn, NY, USA). The ideal alveolar gas equation was used to calculate alveolar oxygen tension and the alveolar to arterial PO_2 difference (A-aDO_2).

2.6. Statistical analysis

Between-group comparisons of subject characteristics including maximal exercise responses were performed using unpaired t-tests. Comparisons of physiological and sensory responses at standardized submaximal work rates were examined using repeated measures ANOVA. To determine if group differences were present at various work rates, the interaction between group and work rate was tested, followed by Bonferroni-adjusted post hoc comparisons when results were significant. Statistical significance was set at $p < 0.05$. Results are reported as means ± SD unless otherwise specified.

3. Results

3.1. Subjects

Subject characteristics are reported in Table 1. Obese asthmatics and normal weight asthmatics were well matched for age, height, and years with asthma. Obese asthmatics included nine obese class I (BMI 30.0–34.9 kg/m^2) and five obese class II (BMI 35.0–39.9 kg/m^2). All obese subjects had body mass values $\geq$ 120% of ideal body

Table 1
Subject characteristics.

	Obese asthmatics (n = 14)	Normal weight asthmatics (n = 14)	p value
Age, years	33 ± 6	32 ± 7	0.78
Sex (M:F)	6:8	5:9	–
Mass, kg	86 ± 14*	59 ± 7	<0.0001
Height, cm	160 ± 11	162 ± 10	0.67
Body mass index, kg/m^2	33 ± 3*	23 ± 1	<0.0001
Asthma, years	13 ± 5	14 ± 5	0.88
Asthma control test	24 ± 1	24 ± 1	0.19
IPAQ-SF walking, min/week	55 ± 30*	89 ± 42	0.02
SaO_2, %	93 ± 3*	95 ± 1	<0.01
PaO_2, mmHg	66 ± 7*	75 ± 4	<0.001
$PaCO_2$, mmHg	31 ± 3*	28 ± 3	0.03
A-aDO_2, mmHg	9 ± 5*	5 ± 3	<0.01
Pulmonary function			
pre-bronchodilator:			
FEV_1, l	3.2 ± 0.8	3.3 ± 0.9	0.69
FEV_1, %predicted	91 ± 9	98 ± 11	0.08
FVC, l	3.9 ± 1.1	4.1 ± 1.1	0.62
FVC, %predicted	92 ± 9*	100 ± 12	0.04
FEV_1/FVC, %	83 ± 7	82 ± 6	0.55
post-bronchodilator:			
FEV_1, l	3.3 ± 0.8†	3.5 ± 0.9†	0.60
FVC, l	3.9 ± 1.1	4.1 ± 1.1	0.64
FEV_1/FVC, %	85 ± 6†	84 ± 6†	0.81
ΔFEV_1, %	3 ± 4	5 ± 3	0.24
ΔFEV_1, ml	100 ± 132	136 ± 89	0.40

Abbreviations: IPAQ-SF, International Physical Activity Questionnaire – short form; SaO_2, arterial oxygen saturation at rest; PaO_2, arterial partial pressure of oxygen at rest; $PaCO_2$, arterial partial pressure of carbon dioxide at rest; A-aDO_2, alveolar to arterial oxygen difference at rest; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity. Note that all measurements were performed at an altitude of ~2,240 m. Values are mean ± SD. * significantly different from normal weight asthmatics, $p < 0.05$; † Significantly different from pre-bronchodilator value, $p < 0.05$.

mass [29]. Both groups were physically inactive with the obese asthmatics reporting significantly less time walking than normal weight asthmatics. Obese asthmatics had significantly worse resting pulmonary gas exchange relative to normal weight asthmatics. Both groups were well matched for baseline spirometry although obese asthmatics had a significantly lower %predicted FVC. Post-bronchodilator FEV_1 and FEV_1/FVC were increased significantly and to a similar degree relative to pre-bronchodilator values in both groups. However, the magnitude of reversibility was within normal limits confirming that both groups had well controlled asthma. All obese asthmatics and normal weight asthmatics regularly used respiratory medications to control their asthma including long-acting β_2-agonist and inhaled corticosteroid combination therapy (n = 10 and 7, respectively), inhaled corticosteroid monotherapy (n = 4 and 7, respectively), and short-acting β_2-agonist as needed (n = 13 and 8, respectively).

3.2. Exercise performance and cardiorespiratory fitness

Maximal exercise data are reported in Table 2. Both groups achieved similar absolute maximal work rates but the obese asthmatics achieved a lower age-, height-, sex-, and mass-predicted work rate. Maximal aerobic capacity (VO_2max) was identical between groups when expressed in l/min but was significantly reduced in obese asthmatics when expressed in ml/kg/min or as % predicted. The anaerobic threshold occurred at a lower percentage of predicted VO_2max (54 ± 15 vs. 66 ± 16 %predicted, $p < 0.05$) in obese asthmatics vs. normal weight asthmatics, respectively.

3.3. Ventilatory and pulmonary gas exchange responses

Ventilatory responses were not different between groups at rest and throughout exercise (Fig. 1). The ratio between maximal minute ventilation (V_E) and the measured MVV (V_E/MVV) was 59 ± 15% and 52 ± 12% in the obese asthmatics and normal weight asthmatics, respectively ($p = 0.17$), with only one obese subject showing evidence of a ventilatory limitation at maximal exercise (i.e., V_E/MVV≥85%) [30]. Pulmonary gas exchange data at maximal exercise are shown in Table 2. Maximal exercise arterial oxygen saturation (SaO_2) and arterial partial pressure of oxygen (PaO_2) were significantly lower and the A-aDO_2 was significantly higher at maximal exercise in the obese asthmatics. These differences primarily reflected group differences at rest since the change in these parameters from rest to maximal exercise was similar between groups.

3.4. Cardiovascular responses

HR and oxygen pulse responses are shown in Fig. 2. No significant differences were observed at rest and throughout exercise. Absolute and age-predicted HR tended to be lower and HR reserve higher in obese asthmatics at maximal exercise but this did not reach statistical significance (Table 2).

3.5. Sensory responses

Sensory responses to exercise are shown in Fig. 3. Dyspnoea intensity ratings were not different at standardized absolute work rates or levels of V_E. Leg fatigue ratings were significantly higher at most submaximal work rates in obese asthmatics compared with normal weight asthmatics.

4. Discussion

The main findings of this study are as follows: 1) Obese individuals with well controlled asthma had significantly reduced cardiorespiratory fitness and were less physically active compared to normal weight asthmatics; 2) Obesity was not associated with alterations in the ventilatory, pulmonary gas exchange, or cardiovascular responses to cycle exercise in well controlled asthmatics;

Table 2
Maximal exercise responses.

	Obese asthmatics (n = 14)	Normal weight asthmatics (n = 14)	p value
Power, W	131 ± 47	134 ± 35	0.86
Power, W/kg	1.5 ± 0.4*	2.2 ± 0.4	<0.0001
Power, % predicted	75 ± 8*	89 ± 13	<0.01
VO_2, ml/kg/min	21.9 ± 5.3*	31.8 ± 5.6	<0.0001
VO_2, l/min	1.9 ± 0.7	1.9 ± 0.5	0.95
VO_2, % predicted	82 ± 14*	92 ± 10	0.04
VCO_2, l/min	2.1 ± 0.7	2.2 ± 0.6	0.87
V_E/VCO_2	34 ± 4	35 ± 5	0.50
V_E/VO_2	38 ± 6	40 ± 6	0.39
RER	1.12 ± 0.06	1.14 ± 0.06	0.36
V_E, l/min	72 ± 22	76 ± 23	0.59
V_E/MVV, %	59 ± 15	52 ± 12	0.17
V_T, l	2.0 ± 0.7	2.0 ± 0.6	0.92
Fb, breaths/min	37 ± 7	40 ± 10	0.52
VO_2/HR, ml/beat	11.5 ± 3.1	10.8 ± 2.3	0.52
VO_2/HR, %predicted	95 ± 16	100 ± 14	0.37
HR, beats/min	164 ± 16	175 ± 14	0.07
HR, %predicted	87 ± 7	92 ± 7	0.06
HRR, beats/min	24 ± 14	15 ± 12	0.05
SaO_2, %	92 ± 3*	94 ± 2	0.01
ΔSaO_2, %	−1 ± 3	−1 ± 2	0.97
PaO_2, mmHg	69 ± 6*	78 ± 5	<0.001
ΔPaO_2, mmHg	2 ± 7	3 ± 6	0.92
$PaCO_2$, mmHg	30 ± 3*	27 ± 2	0.02
$\Delta PaCO_2$, mmHg	−1 ± 3	−1 ± 4	0.95
A-aDO_2, mmHg	17 ± 5*	11 ± 4	<0.01
ΔA-aDO_2, mmHg	8 ± 8	6 ± 6	0.59
Blood Lactate, mmol/l	8.4 ± 3.0	9.6 ± 2.8	0.30

Abbreviations: VO_2, oxygen consumption; VCO_2, carbon dioxide production; V_E/VCO_2, ventilatory equivalent for carbon dioxide; V_E/VO_2, ventilatory equivalent for oxygen; RER, respiratory exchange ratio; V_E, minute ventilation; MVV, maximum voluntary ventilation; V_T, tidal volume; Fb, breathing frequency; VO_2/HR, oxygen pulse; HR, heart rate; HRR, heart rate reserve; SaO_2, arterial oxygen saturation; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; A-aDO_2, alveolar to arterial oxygen difference; Δ, change from rest (i.e., the difference between rest and maximal exercise). Values are mean ± SD, * significantly different from normal weight asthmatics, $p < 0.05$.

3) Dyspnoea intensity was similar between groups but obese asthmatics had significantly elevated leg fatigue ratings throughout exercise.

4.1. Cardiorespiratory fitness

Assessing cardiorespiratory fitness in obese individuals poses several interpretive challenges because of the confounding influence of increased body mass on VO_2max. VO_2max, the gold standard measurement of cardiorespiratory fitness, is typically expressed in absolute values (l/min) or relative to body mass (ml/kg/min) or lean body mass (ml/LBM/min). The increased body mass of obese individuals places them at a significant disadvantage when VO_2max values are reported using conventional units (i.e., ml/kg/min). Thus, cardiorespiratory fitness may be substantially underestimated in obese individuals. We have shown that VO_2max values are similar between groups when reported in l/min but are significantly lower in the obese subjects when reported relative to body mass (Table 2), a finding consistent with other studies [31,32]. To overcome this interpretive challenge, Lorenzo et al. [31] recently recommended that VO_2max should be expressed relative to predicted values using established equations. They argue that cardiorespiratory fitness in obese individuals is related to their height and estimated "normal" (i.e., predicted) mass than to their total mass [31,33]. We used equations specific to obese and non-obese individuals from Wasserman et al. [29] which adjusts the predicted VO_2max to account for the increased metabolic requirements of unloaded exercise in obese subjects. To our knowledge this is the first study to use this approach in individuals with combined obesity and asthma. Our results suggest that %predicted VO_2max is significantly lower in obese asthmatics vs. normal weight asthmatics. The anaerobic threshold also occurred at a lower %predicted VO_2max, further indicating reductions in cardiorespiratory fitness. To examine the potential mechanisms for the reduced cardiorespiratory fitness in obese asthmatics, we performed a detailed analysis of ventilatory, pulmonary gas exchange, cardiovascular, and sensory responses during cycle exercise.

4.2. Ventilatory responses

We previously demonstrated that ventilatory responses are preserved in normal weight asthmatics relative to age-, BMI-, and activity-matched non-asthmatics [20]. We reasoned that the combined effects of obesity and asthma might predispose our obese subjects to greater ventilatory limitations and altered breathing pattern responses during exercise as shown previously in obese subjects without co-existing pulmonary conditions [19]. However, the results of the present study demonstrate that mild-to-moderate obesity was not associated with alterations in the ventilatory response to exercise. Both groups achieved a maximal V_E/MVV<85% suggesting that our subjects did not have evidence of a "ventilatory limitation" [30]. This widely used, albeit crude method of assessing ventilatory limitations does not provide information regarding the nature or source of the ventilatory constraint. Alternative approaches (e.g. flow volume loop analysis and operating lung volumes) provide more direct evidence of ventilatory limitations during exercise [34]. However, given the substantial ventilatory reserve and low dyspnoea ratings in both groups (Fig. 3), it is unlikely that these additional measurements would reveal compelling evidence of ventilatory limitations in our subjects. Moreover, both groups had an adequate hyperventilatory response as reflected by their reduced arterial partial pressure of carbon dioxide at maximal exercise (Table 2). Previous studies have reported a slightly more rapid and shallow breathing response in

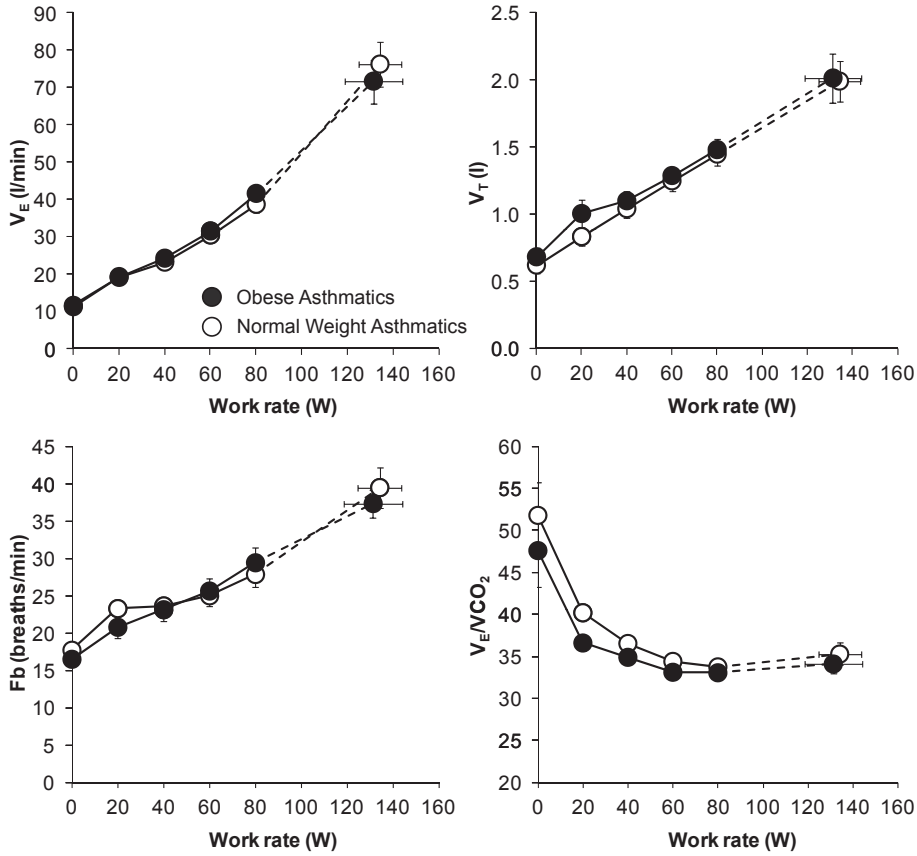

Fig. 1. Ventilatory responses to exercise in obese asthmatics and normal weight asthmatics. Abbreviations: V_E, minute ventilation; V_T, tidal volume; Fb, breathing frequency; V_E/VCO_2, ventilatory equivalent for carbon dioxide. Values are mean ± SEM.

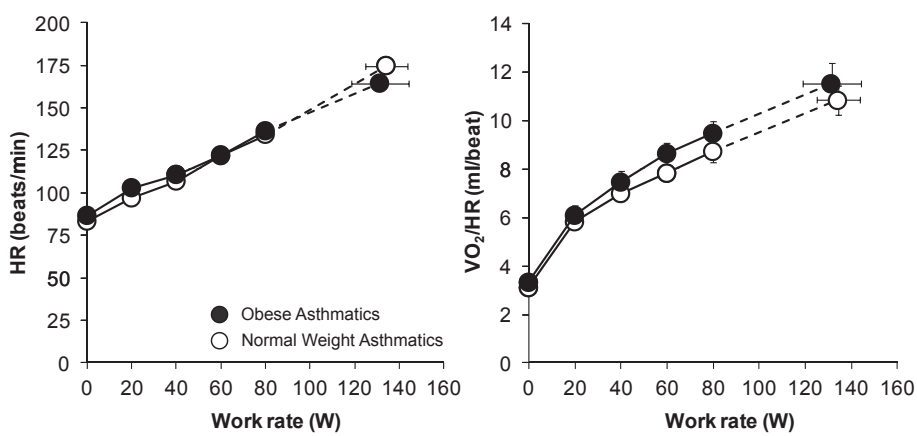

Fig. 2. Cardiovascular responses to exercise in obese asthmatics and normal weight asthmatics. Abbreviations: HR, heart rate; VO_2/HR, oxygen pulse. Values are mean ± SEM.

obese subjects compared to normal weight controls [18,19], a finding that was not observed in the present study. The preserved breathing pattern responses in our obese asthmatics coupled with the low V_E/MVV at maximal exercise suggests that ventilatory responses are preserved in individuals with mild-to-moderate obesity and well controlled asthma. Thus, superimposing obesity on asthma did not place the respiratory system at a major disadvantage during exercise and cannot be used as an explanation for the relatively reduced cardiorespiratory fitness in our obese subjects.

4.3. Pulmonary gas exchange

Few studies have examined pulmonary gas exchange responses using arterial sampling during exercise in subjects with mild-to-moderate obesity and to our knowledge; there are no studies that have measured arterial blood gases during exercise in individuals with combined obesity and well controlled asthma. While there were statistically significant differences in arterial blood-gas values between groups at rest (Table 1), this was not considered to be clinically meaningful as the values were similar to normative data

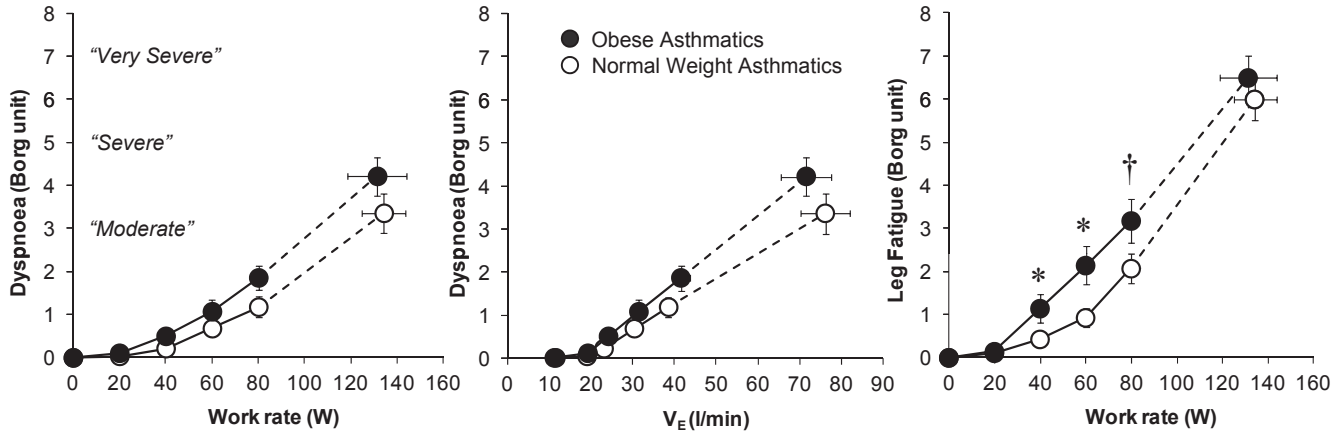

Fig. 3. Sensory responses to exercise in obese asthmatics and normal weight asthmatics. Abbreviations: V_E, minute ventilation. Values are mean ± SEM. *$p < 0.05$; †$p = 0.08$.

collected at the same altitude [35]. Even at peak exercise in the present study, the A-aDO_2 was considered normal (i.e., <25 mmHg [36]), despite statistically significant differences between groups. Importantly, there was no evidence of clinically important arterial desaturation in either group as the change in SaO_2 from rest to maximal exercise was only ~1% in both groups. The V_E/VCO_2 was superimposed at rest and during exercise suggesting that obesity was not associated with greater ventilatory inefficiency, a finding consistent with other studies in obese subjects [19]. Given the preservation of SaO_2 from rest to maximal exercise, it seems reasonable to conclude that pulmonary gas exchange abnormalities do not contribute importantly to the reduced cardiorespiratory fitness in obese asthmatics. Collectively, the similarities in the ventilatory and pulmonary gas exchange responses indicate that the respiratory system is not the limiting factor to exercise performance in obese asthmatics.

4.4. Cardiovascular responses

Both groups achieved maximal HR values that approached their age-predicted values. The HR and oxygen pulse responses were also similar between groups throughout all submaximal exercise intensities (Fig. 2). There was a tendency for the obese subjects to achieve a slightly lower absolute HR and a greater HR reserve at maximal exercise but these differences were not statistically significant. We do not believe this reflects poor effort on the part of our obese subjects because they achieved maximal respiratory exchange ratio values in excess of 1.10 [30] and reported "very severe" leg discomfort ratings at volitional exhaustion.

4.5. Sensory responses

Previous work in normal weight asthmatics and controls found similar dyspnoea intensity ratings during cycle exercise [20]. We hypothesized that the combination of obesity and asthma might predispose obese asthmatics to greater dyspnoea relative to normal weight asthmatics. However, this was not the case. Perhaps this is not surprising given that the ventilatory responses during exercise were identical between groups (Fig. 1). Ofir et al. [19] conducted a careful evaluation of dyspnoea in obese and non-obese women and found higher levels of dyspnoea for a given cycle work rate in their obese subjects. The higher dyspnoea intensity ratings reflected the increased metabolic cost of cycling and the corresponding increase in V_E in their obese subjects. However, the authors acknowledged that only "slight" breathing discomfort (2 out of 10 on the Borg scale) was measured in their obese subjects, even when exercising at 80% of their predicted maximum work rate. We did not observe an increase in metabolic or ventilatory requirements for a given cycle work rate as has been shown previously in obese individuals during exercise [19,37]. This discrepancy may be attributable, at least in part, to differences in BMI across studies and due to unmeasured differences in adipose tissue distribution. Regardless, our results in combination with the work of others [19,38] suggest that combined obesity and well controlled asthma does not have a major impact on dyspnoea.

In contrast to our dyspnoea data, ratings of perceived leg fatigue were consistently elevated in obese asthmatics to perform the same standardized physical task relative to normal weight asthmatics. Increases in perceived leg fatigue in obese individuals is thought to reflect the higher contractile muscle effort requirements and central motor command output needed to move heavier limbs during cycling [19]. However, we do not believe this is the only explanation in our obese asthmatics because VO_2 was not greater for a given absolute work rate compared to controls. Rather, we speculate that the higher ratings of leg fatigue and the relatively reduced cardiorespiratory fitness in our obese asthmatics reflects greater deconditioning. We intentionally recruited sedentary individuals in this study but still observed significantly lower levels of activity in our obese subjects based on walking time. It is possible that the extreme inactivity in our obese asthmatics prevented the skeletal muscle hypertrophy that often occurs in obese subjects as an adaptation to sustained mass loading from excessive adipose tissue. However, this remains speculative as muscle mass was not measured in this study.

4.6. Limitations

We defined obesity based on BMI which has well established limitations. The lack of body composition measurements precludes us from determining the role of body fat distribution as an explanation for some of our findings. It is important to acknowledge that our results are limited to individuals with mild-to-moderate obesity and well controlled asthma during weight supported cycle exercise. Consequently, we cannot extrapolate our findings to those with greater degrees of obesity, those with poorly controlled asthma, and individuals exercising during weight-bearing exercise. Finally, our exercise tests were performed at moderate altitude and therefore our predicted VO_2 values may be slightly lower than if the tests were performed at sea-level. Regardless, we used a normal weight asthmatic control group as the primary source of

comparison rather than basing our conclusions on absolute %predicted VO_2 values in the obese asthmatics.

5. Conclusions

Obese asthmatics have reduced cardiorespiratory fitness, greater physical inactivity levels, and increased leg discomfort ratings during cycle exercise compared to well matched normal weight asthmatics. The reduced cardiorespiratory fitness could not be explained by differences in the ventilatory, pulmonary gas exchange, or cardiovascular responses to exercise. The well preserved physiological responses to exercise in obese asthmatics coupled with their reduced anaerobic threshold points to greater deconditioning associated with extreme physical inactivity as the primary cause of their low cardiorespiratory fitness.

Conflicts of interest and sources of support

None of the authors have any conflicts of interest to report. JG was supported by a Scholar Award from the Michael Smith Foundation for Health Research and a New Investigator Award from the Providence Health Care Research Institute and St. Paul's Hospital Foundation.

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References

[1] J.B. Dixon, The effect of obesity on health outcomes, Mol. Cell Endocrinol. 316 (2010) 104–108.
[2] D.P. Guh, W. Zhang, N. Bansback, Z. Amarsi, C.L. Birmingham, A.H. Anis, The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis, BMC Public Health 9 (2009) 88.
[3] E.R. Sutherland, Linking obesity and asthma, Ann. N. Y. Acad. Sci. 1311 (2014) 31–41.
[4] S.H. Kim, E.R. Sutherland, E.W. Gelfand, Is there a link between obesity and asthma? Allergy Asthma Immunol. Res. 6 (2014) 189–195.
[5] Y.C. Chen, G.H. Dong, K.C. Lin, Y.L. Lee, Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis, Obes. Rev. 14 (2013) 222–231.
[6] E.S. Ford, The epidemiology of obesity and asthma, J. Allergy Clin. Immunol. 115 (2005) 897–909.
[7] J.C. Celedon, L.J. Palmer, A.A. Litonjua, S.T. Weiss, B. Wang, Z. Fang, et al., Body mass index and asthma in adults in families of subjects with asthma in Anqing, China, Am. J. Respir. Crit. Care Med. 164 (2001) 1835–1840.
[8] Y. Chen, R. Dales, D. Krewski, K. Breithaupt, Increased effects of smoking and obesity on asthma among female Canadians: the National Population Health Survey, 1994-1995, Am. J. Epidemiol. 150 (1999) 255–262.
[9] S.O. Shaheen, J.A. Sterne, S.M. Montgomery, H. Azima, Birth weight, body mass index and asthma in young adults, Thorax 54 (1999) 396–402.
[10] S. Kim, C.A. Camargo Jr., Sex-race differences in the relationship between obesity and asthma: the behavioral risk factor surveillance system, 2000, Ann. Epidemiol. 13 (2003) 666–673.
[11] D.A. Beuther, E.R. Sutherland, Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies, Am. J. Respir. Crit. Care Med. 175 (2007) 661–666.
[12] W. Nystad, H.E. Meyer, P. Nafstad, A. Tverdal, A. Engeland, Body mass index in relation to adult asthma among 135,000 Norwegian men and women, Am. J. Epidemiol. 160 (2004) 969–976.
[13] D.R. Gold, A.I. Damokosh, D.W. Dockery, C.S. Berkey, Body-mass index as a predictor of incident asthma in a prospective cohort of children, Pediatr. Pulmonol. 36 (2003) 514–521.
[14] K. Hakala, B. Stenius-Aarniala, A. Sovijarvi, Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma, Chest 118 (2000) 1315–1321.
[15] B. Simard, H. Turcotte, P. Marceau, S. Biron, F.S. Hould, S. Lebel, et al., Asthma and sleep apnea in patients with morbid obesity: outcome after bariatric surgery, Obes. Surg. 14 (2004) 1381–1388.
[16] B. Stenius-Aarniala, T. Poussa, J. Kvarnstrom, E.L. Gronlund, M. Ylikahri, P. Mustajoki, Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study, BMJ 320 (2000) 827–832.
[17] S.D. Aaron, D. Fergusson, R. Dent, Y. Chen, K.L. Vandemheen, R.E. Dales, Effect of weight reduction on respiratory function and airway reactivity in obese women, Chest 125 (2004) 2046–2052.
[18] T.G. Babb, D.S. DeLorey, B.L. Wyrick, P.P. Gardner, Mild obesity does not limit change in end-expiratory lung volume during cycling in young women, J. Appl. Physiol. 92 (2002) 2483–2490.
[19] D. Ofir, P. Laveneziana, K.A. Webb, D.E. O'Donnell, Ventilatory and perceptual responses to cycle exercise in obese women, J. Appl. Physiol. 102 (2007) 2217–2226.
[20] A. Cortes-Telles, L. Torre-Bouscoulet, R. Mejia-Alfaro, M. Silva-Ceron, S.S. Wilkie, J.A. Guenette, Cardiorespiratory and sensory responses to exercise in well controlled asthmatics, J. Asthma 52 (2015) 576–582.
[21] National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, National Institutes of Health, Bethesda, MD, 2007. Report 07–4051. Available from: http://www.ncbi.nlm.nih.gov/books/NBK7232/. Last access: 15.02.15.
[22] R. Pellegrino, G. Viegi, V. Brusasco, R.O. Crapo, F. Burgos, R. Casaburi, et al., Interpretative strategies for lung function tests, Eur. Respir. J. 26 (2005) 948–968.
[23] J.P. Parsons, T.S. Hallstrand, J.G. Mastronarde, D.A. Kaminsky, K.W. Rundell, J.H. Hull, et al., An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction, Am. J. Respir. Crit. Care Med. 187 (2013) 1016–1027.
[24] Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), 2014. Available from: http://www.ginasthma.org/. Last access: 15.02.15.
[25] M.R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, et al., Standardisation of spirometry, Eur. Respir. J. 26 (2005) 319–338.
[26] R. Perez-Padilla, G. Valdivia, A. Muino, M.V. Lopez, M.N. Marquez, M. Montes de Oca, et al., Spirometric reference values in 5 large Latin American cities for subjects aged 40 years or over, Arch. Bronconeumol. 42 (2006) 317–325.
[27] W.L. Beaver, K. Wasserman, B.J. Whipp, A new method for detecting anaerobic threshold by gas exchange, J. Appl. Physiol. 60 (1986) 2020–2027.
[28] N.L. Jones, Clinical Exercise Testing, third ed., W.B. Saunders, Philadelphia, PA, 1988.
[29] K. Wasserman, J.E. Hansen, D.Y. Sue, W.W. Stringer, B.J. Whipp, Normal Values. Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications, fourth ed., Lippincott Williams & Wilkins, Philadelphia, PA, 2005.
[30] M.K. Stickland, S.J. Butcher, D.D. Marciniuk, M. Bhutani, Assessing exercise limitation using cardiopulmonary exercise testing, Pulm. Med. 2012 (2012) 824091.
[31] S. Lorenzo, T.G. Babb, Quantification of cardiorespiratory fitness in healthy nonobese and obese men and women, Chest 141 (2012) 1031–1039.
[32] T.G. Babb, E.R. Buskirk, J.L. Hodgson, Exercise end-expiratory lung volumes in lean and moderately obese women, Int. J. Obes. 13 (1989) 11–19.
[33] M. Younes, Interpretation of clinical exercise testing in respiratory disease, Clin. Chest Med. 5 (1984) 189–206.
[34] J.A. Guenette, R.C. Chin, J.M. Cory, K.A. Webb, D.E. O'Donnell, Inspiratory capacity during exercise: measurement, analysis, and interpretation, Pulm. Med. 2013 (2013) 956081.
[35] S.O. Perez Martinez, J.R. Perez-Padilla, Gasometric values reported in healthy subjects from the Mexican population: review and analysis, Rev. Invest. Clin. 44 (1992) 353–362.
[36] J.A. Dempsey, P.D. Wagner, Exercise-induced arterial hypoxemia, J. Appl. Physiol. 87 (1999) 1997–2006.
[37] J.A. Dempsey, W. Reddan, B. Balke, J. Rankin, Work capacity determinants and physiologic cost of weight-supported work in obesity, J. Appl. Physiol. 21 (1966) 1815–1820.
[38] A. Deesomchok, T. Fisher, K.A. Webb, J. Ora, Y.M. Lam, M.D. Lougheed, et al., Effects of obesity on perceptual and mechanical responses to bronchoconstriction in asthma, Am. J. Respir. Crit. Care Med. 181 (2010) 125–133.