SEX DIFFERENCES IN EXERCISE-INDUCED FLOW LIMITATION IN PREPUBESCENT CHILDREN: PREVALENCE AND IMPLICATIONS

by

KATHERINE E. SWAIN

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Approved by:

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Major Professor
Craig A. Harms, PhD

Abstract

In comparison to adults and adolescents, relatively little is known about ventilatory responses of prepubescent children to exercise. Children have smaller airways relative to lung size than adults and ventilate "out of proportion" to metabolic demands of exercise which may render them more susceptible to ventilatory limitations during exercise. It is also not known if there are any sex differences in ventilatory limitations during incremental exercise in children. Therefore, the purpose of this study was to determine the prevalence of ventilatory constraints (expiratory flow limitation, EFL) during incremental exercise to exhaustion in prepubescent (Tanner stage 1) boys and girls. Forty healthy, prepubescent boys (n = 20) and girls (n = 20) with no history of asthma completed baseline pulmonary function and lung volume tests. Subjects then completed an incremental cycle VO_{2max} test where workload was increased 10W every 90 sec until exhaustion. RPE, dyspnea ratings, and % EFL were recorded at the end of each exercise stage. EFL was determined by placing the exercising tidal volume loop inside a post-exercise maximal flow volume envelope. Ventilatory and metabolic data were recorded on a breath by breath basis throughout exercise via a metabolic cart. Arterial oxygen saturation was determined via pulse oximetry. Body composition was determined using dual-energy x-ray absorptiometry. Following 15 minutes of recovery, subjects exercised at 105% of their VO_{2max} workload until exhaustion to provide confident in the VO_{2max} measurement. There were no differences ($p>0.05$) in anthropometric measures (height, weight) or body composition (lean body mass, percent body fat) measures between boys and girls. At rest, boys had significantly higher lung volumes (TLC, boys = 2.6 + 0.5 L, girls = 2.1 $\pm$ 0.5 L; FRC, boys = 0.9 $\pm$ 0.3 L, girls =

0.7 ± 0.3 L) and maximal flows (FVC, boys = 2.2 ± 0.3 L, girls = 1.9 ± 0.4 L; PEF, boys = 3.6 ± 0.7 L/sec, girls = 2.9 ± 0.6 L/sec; FEV_1, boys = 1.9 ± 0.2 L/sec, girls = 1.6 ± 0.3 L/sec). At maximal exercise, boys had significantly higher VO_{2max} (boys = 35.4 ± 7.5 ml/kg/min, girls = 29.5 ± 6.6 ml/kg/min; boys = 1.2 ± 0.2 L/min, girls = 1.0 ±0.2 L/min), V_E (boys = 49.8 ± 8.8 L/min, girls = 41.2 ± 8.3 L/min), and VCO_2 (boys = 1.2 ± 0.2 L/min, girls = 0.9 ± 0.2 L/min) compared to girls. There were no differences ($p>0.05$) in V_E/VCO_2 (boys = 41.1 ± 3.9, girls = 43.4 ± 5.5), $P_{ET}CO_2$ (boys = 35.5 ± 2.5 mmHg, girls = 35.7 ± 3.2 mmHg) maximal HR (boys = 174.4 ± 23.1 bpm; girls = 183.4 ± 16.6 bpm), RER (boys = 1.04 ± 0.05, 1.03 ± 0.08), or SaO_2 (boys = 96.7 ± 3.4%, girls = 97.7 ± 1.3%) which was maintained within 3% of baseline throughout exercise for all subjects. EFL during exercise was present in 19 of 20 boys and 18 of 20 girls. Severity of EFL at VO_{2max}, as judged by % overlap of tidal volume with maximal flow volume envelope, was not different between genders at any time during exercise (at VO_2max: boys = 58 ± 7%, girls = 43 ± 8%). There was no significant association between % EFL at VO_{2max} and aerobic capacity or total lung volume. A significant relationship existed between % EFL at VO_{2max} and the change in end-expiratory lung volume from rest to maximal exercise in boys ($r = 0.77$) and girls ($r = 0.75$). In summary, our data suggests that ventilatory constraints in the form of expiratory flow limitation are highly and equally prevalent in prepubescent boys and girls from moderate to maximal exercise which likely leads to an increased work of breathing, but not to decreases in arterial oxygen saturation.

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CHAPTER 1 - LITERATURE REVIEW

Introduction

Important sex differences exist in structure and resting pulmonary function that may affect ventilation and gas exchange during exercise. Adult men have larger airway diameters, larger lung volumes and diffusion surfaces when compared to height-matched adult women (Crapo et al, 1982; Guenette et al, 2007). Given these structural differences, it has been suggested that women utilize a greater proportion of ventilatory reserve relative to the metabolic demand of exercise. It is likely that these sex differences contribute to greater ventilatory limitations and gas exchange disturbances during exercise in women.

Sex differences are also apparent in children before puberty. Boys have larger lungs than girls for the same stature, resulting in a larger number of total alveoli and a larger alveolar surface area (Thurlbeck, 1980). A complex relationship exists between sex and anthropometric measures in predicting lung function (Schwartz et al, 1988; Wang et al, 1993). Boys also have greater aerobic capacity (Dencker et al, 2007), indicating a greater maximal metabolic demand.

Prepubescent children exhibit smaller airways relative to lung size than adults and also ventilate out of proportion to metabolic demand during exercise (Cooper et al, 1987). By reaching high levels of ventilation, children may meet ventilatory mechanical limits more easily during exercise. In fact, expiratory flow limitation (EFL) has been documented in prepubescent children, but discrepancies exist in explaining prevalence in this population (Nourry et al, 2005). Also, it is not known if there is a sex difference in expiratory flow limitation (EFL) during exercise. This review will initially focus on

normal sex differences in ventilatory limitations in adults, followed by a discussion on sex differences in ventilatory limitations in healthy, prepubescent children.

Sex Differences during Exercise

Basis for Pulmonary Function Differences

The basis for sex differences in pulmonary function and exercise tolerance is primarily due to hormonal and structural/morphological differences. Regarding hormones, changes in circulating levels of progesterone and estrogen during the menstrual cycle can affect pulmonary function during exercise. Progesterone affects pulmonary function by stimulating ventilation (Moore et al, 1987), increasing hypercapnic ventilatory response (HCVR), and increasing hypoxic ventilatory response (HVR) (Moore et al, 1987). Most importantly, progesterone may affect central ventilatory drive, and breathing responsiveness during exercise (Dombovy et al, 1987). Although these findings may help explain sex differences in airway responsiveness, the role of female hormones in pulmonary function is complex and not yet fully understood.

More recently, the role of adiposity on pulmonary function has gained increased attention, given the substantial rise of obesity in the United States. After adjusting for height, adult males have greater total lean body mass and less total fat mass than adult women (Wells, 2007). Tissue distribution also differs by gender; men have greater muscle mass in arms, less fat mass in their limbs, and similar values of central adiposity (Wells, 2007). Females have greater fat mass in peripheral tissues in early adulthood, but after menopause, there is a trend for women to acquire a more android fat distribution. These body composition differences are primarily a consequence of steroid hormones that manifest during puberty and menopause. Thyagarajan et al (2008) studied a cohort

of 5,115 adults for 10 years to evaluate lung function relative to obesity, as determined by body mass index (BMI). Obesity was defined as having a BMI of > 30 kg/m^2. The authors found that among young adults (ages 18-30), increasing BMI in initially thin participants (BMI< 21.3 kg/m^2) was associated with increasing, then stabilizing lung function, as estimated by forced vital capacity (FVC), through age 38. Conversely, individuals who gained the most weight over 10 years had the largest decrease in forced vital capacity (FVC). FEV_1 decreased with increasing weight gain in all participants with maximum decline in obese individuals who gained the most weight during the study. Chen et al (1993) reported similar declines in lung volumes associated with weight gain. When sex differences were included, the effect of weight gain on pulmonary function was greater in men than women.

There are apparent sex differences in structural and functional capacity of the lung and chest wall. While the young, healthy adult male's respiratory system is "overbuilt" with regard to flow rate, lung volume, and O_2 and CO_2 exchange (Harms et al, 1999), women may differ. It has been documented that height-matched men have larger airway diameter (Mead, 1980), larger lung volumes and diffusion surfaces (Schwartz et al, 1988, Thurlbeck, 1982) compared to postpubertal women. Sitting height or differences in trunk length can account for some, but not all, sex differences in lung volumes and maximal expiratory flow rates in healthy adults. There does not seem to be a difference between sexes in elastic properties of the lungs (Rohrbach et al, 2003) and chest wall or pulmonary compliance (Johnson et al, 1993). Given structural disadvantages in women, combined with the inability of the pulmonary system to "adapt" to training, women may therefore be more susceptible to pulmonary limitations during exercise compared to men for a given metabolic demand.

Aerobic Capacity

Maximal oxygen uptake (VO_{2max}) reflects the highest aerobic metabolic rate available for energy turnover. VO_{2max} relies on respiratory, hemodynamic, and metabolic factors, more specifically oxidative enzymatic activity in exercising muscle. This measure has been used in clinical settings to predict aerobic capacity and energy expenditure (Goran and Poehlman, 1992). Maximal oxygen uptake is usually expressed relative to total body mass or lean body mass (LBM); by making the measure size independent, comparisons can be made between persons of different sizes, and between genders. Davis et al (2007) compared VO_{2max} at the same lean body mass in 230 sedentary men and women ranging in age from 20-70 years (115 males, 113 females). By controlling for physical activity levels, and using LBM as a covariate, the authors found that VO_{2max} for the same LBM was higher in sedentary men than sedentary women. The mean VO_{2max} value for men was 30% greater than for sedentary women. Much of the sex difference in VO_{2max} is likely due to a larger oxygen carrying capacity in arterial blood in men compared to women (Brooks et al, 1996).

Pulmonary Response to Exercise

Because of important structural differences between sexes that have been previously described, two important distinctions in the ventilatory response to exercise exist. First, women have a similar ratio of tidal volume to vital capacity (V_{Tmax}/VC) compared to men, however, both values are smaller, so women reach their V_{Tmax} at a relatively smaller VC (McClaran et al, 1998). Given the earlier plateau of V_{Tmax}, women must therefore compensate by depending on a higher frequency of breathing. Second, smaller airways and lung volumes indicate that women often have smaller maximal flow-

volume loops than men, which leads to increased ventilatory constraints during exercise (McClaran et al, 1998).

Although a substantial reserve exists for increases in ventilation during maximal exercise in healthy untrained men (Dempsey et al, 1984), based on women's smaller airway dimensions and a relatively high demand during exercise, it is possible that their reserve is encroached upon earlier and/or more than men's reserve. To evaluate maximal available ventilation, McClaran et al (1998) calculated maximal ventilatory capacity (V_{Ecap}) and maximal voluntary ventilation (MVV). V_{Ecap} was estimated by the relationship between maximal flow-volume loop (MFVL) and V_T at maximal exercise. MVV was calculated as an extrapolation of 12 seconds of maximal voluntary effort to one minute. Ratios of V_{Emax}/V_{Ecap} and V_{Emax}/MVV indicated that both surpassed 80% at a V_E of 110 liters per minute in women. Women reach this percentage of ventilatory capacity at smaller VO_2 and V_E (McClaran et al, 1998), meaning women have an increased ventilatory response to exercise and use a greater proportion of their maximal available ventilation compared to men.

Limitations During Exercise

Expiratory Flow Limitation

The pulmonary system does not usually limit exercise tolerance in normal, healthy individuals. However, women seem to be more susceptible to pulmonary limitations (ventilatory constraints) during exercise due to smaller pulmonary capacity relative to men. Expiratory flow limitation (EFL) is expressed as the percent of a tidal volume loop that meets or exceeds the expiratory boundary of the maximal flow-volume loop (Babb et al, 1991; Johnson et al, 1995). The degree of EFL during exercise has been

described as a balance between ventilatory demand and capacity combined with end-expiratory lung volume (EELV) regulation (Johnson et al, 1999). During exercise, with increased V_E, EELV typically decreases and conversely, end-inspiratory lung volume (EILV) increases (Henke et al, 1988). As EELV decreases, breathing is closer to residual volume (RV) or at a low lung volume where ventilatory reserve is limited, maximal flow is reduced, and chest wall compliance is also reduced. A decrease in EELV requires more force from expiratory muscles whilst optimizing muscle length to generate force. When EFL occurs, EELV typically begins to increase, the tidal volume loop shifts, and EILV approaches total lung capacity (TLC). When EELV increases above resting values, it is termed dynamic hyperinflation (Johnson et al, 1999). Dynamic hyperinflation is not a favorable adaptation in healthy individuals as it decreases inspiratory muscle length, increases the work and oxygen cost of breathing, and therefore, decreases the inspiratory muscle endurance time (Tzelepis et al, 1988). As exercise progresses, much evidence shows that ventilatory constraints worsen (Johnson et al, 1995; Johnson et al, 1991; Aaron et al, 1992). Thus, as the degree of expiratory flow limitation increases, EELV rises and dynamic hyperinflation occurs (Johnson et al, 1999).

Expiratory flow limitation is prevalent in older fit adults (Johnson et al, 1991), highly trained young men (Johnson et al, 1992), women (McClaran et al, 1998), and most recently has been described in prepubescent children (Nourry et al, 2005; Nourry et al, 2006). The prevalence of EFL in women has become more recognized (McClaran et al, 1998, Guenette et al, 2007) as more emphasis is placed on understanding structural and functional differences of women's anatomy compared to men. Guenette et al (2007) recently confirmed the presence of EFL in endurance trained women. The negative expiratory pressure technique was used to compare the flow-volume curve of the

subsequent expiration with the preceding control breath, and an esophageal balloon-tipped catheter measured the work of breathing in male and female highly trained athletes. Results were threefold; female athletes experience EFL more frequently and at a lower V_E compared to males, females experienced greater dynamic hyperinflation during maximal exercise than men, and the total mechanical work of breathing was higher in women compared to men during an incremental exercise test.

Consequences of Expiratory Flow Limitation

Increased EFL and relative dynamic hyperinflation indicate vulnerability for increased oxygen cost of hyperpnea and work of breathing during heavy exercise (Aaron et al, 1992; McClaran et al, 1998; Guenette et al, 2007). Due to a combination of factors, women likely experience greater limitations during heavy exercise than men. For example, women have smaller vital capacity (VC), resulting in a smaller maximal tidal volume (V_{Tmax}), and a higher breathing frequency during heavy exercise, therefore increasing dead space ventilation. Thus, women must maintain a higher level of ventilation to obtain a similar alveolar ventilation compared to men, resulting in less efficient exercise hyperpnea (McClaran et al, 1998). Next, an increased frequency of breathing and shortened expiratory time causes higher expiratory flow rates that increase the possibility and severity of EFL. Lastly, dynamic hyperinflation caused by EFL shortens the initial length of the inspiratory muscles (McClaran et al, 1998). Johnson et al (1992) reported that dynamic hyperinflation caused by EFL had a significant effect on pressure generation by the inspiratory muscles; inspiration occurring at very high lung volumes (EILV/TLC of 86% on average from subjects) increases the elastic load on inspiratory muscles. The combined less efficient hyperpnea and higher respiratory

muscle oxygen requirement in women would suggest important consequences of EFL, including dyspnea, respiratory muscle fatigue and exercise-induced arterial hypoxemia.

Dyspnea

Muscle fatigue has been defined as the decline of muscle responsiveness to its central motor command at high power outputs (Killian, 2006). The increasing intensity of whole body effort and dyspnea are noticeable appearances of fatigue. Perceived exertion intensifies with increasing power and duration of an activity, many times limiting exercise tolerance in a subject due to exertional discomfort from respiratory or peripheral skeletal muscles (Killian, 2006). During whole body exercise, there is sense of discomfort associated with inspiratory muscle activity, and when a subject feels that the discomfort is no longer endurable, exercise tolerance may be compromised. Extreme inspiratory effort may be caused by the increased load on respiratory muscles from added mechanical loads, increased velocity of contraction at shortened muscle length, and mechanical disadvantages imposed by the diaphragm (Killian and Campbell, 1991).

Respiratory Muscle Fatigue

At exercise intensities above 80% VO_{2max}, the diaphragm consistently shows fatigue at the end of exercise, as determined by bilateral phrenic nerve stimulation (Johnson et al, 1993). Sheel et al (2002) reported that at high levels of respiratory work, fatiguing respiratory muscles cause vasoconstriction and reduction in blood flow to the working locomotor muscles. Exercise tolerance may be compromised by decreased locomotor muscle perfusion and oxygen uptake (Harms et al, 1997; Harms et al, 1998). Due to greater EFL, women may be especially vulnerable to increased respiratory muscle fatigue during heavy exercise, requiring increased redistribution of blood flow from the working muscles to the respiratory muscles compared to men.

Exercise-Induced Arterial Hypoxemia and Gas Exchange

Exercise-induced arterial hypoxemia (EIAH) occurs during severe exercise in highly fit humans (Dempsey et al, 1984), some older athletes (Prefaut, 1991), and also in women (Harms et al, 1998b). In women, EIAH has been reported to occur at a lower percent VO_{2max} than men. Contributions to EIAH include the excessive widening of the alveolar arterial oxygen difference (Olfert, 2004), an insufficient ventilatory response (Dempsey and Wagner, 1999; Harms and Stager, 1995), and to a minor extent, intrapulmonary arteriovenous shunts (Eldridge et al, 2004).

As noted in a recent review (Hopkins and Harms, 2004), there are relatively few published studies that have used temperature corrected arterial blood gas data to evaluate pulmonary gas exchange in men and women. Compiled studies (Dempsey et al, 1984; Harms et al, 1998b; Hopkins et al, 2000; Hopkins et al, 1994; Olfert et al, 2004; Rice et al, 1999) revealed that in 57 women (VO_{2max} 32-70 ml/kg/min) and 135 men (VO_{2max} 30-83 ml/kg/min), the slope of the relationship of arterial-alveolar oxygen difference to VO_2, during heavy to maximal exercise, is greater in women. For women and men of the same fitness level (less than 50 ml/kg/min), 12% of women showed gas exchange impairments compared to less than 2% of men. Differences in gas exchange are reflected in PaO_2 data as well; this data indicates that women may be more susceptible to gas exchange impairments than men. However, there is a clear need for more descriptive data in the female population to be certain of these predictions.

It was first shown by Powers et al (1989) that by preventing arterial oxygen desaturation ($\leq$ 92% SaO_2) with a hyperoxic inspirate (26% O_2), VO_{2max} increased in highly trained athletes. Harms et al (2000) investigated the effect of EIAH on VO_{2max} in

women. By preventing oxygen desaturation via a hyperoxic inspirate (26%), a significant increase in VO_{2max} was seen. In fact, VO_{2max} increased in proportion to the amount of desaturation that occurred under normoxic conditions. The authors predicted that the increase in VO_{2max} accomplished by preventing oxygen desaturation is directly from the gain in arterial oxygen content (CaO_2) and directly proportional to the increase in arterial alveolar difference at maximal exercise. The high prevalence of oxygen desaturation in women during submaximal (Harms et al, 1998b) and heavy exercise indicates that exercise tolerance may be affected.

Pulmonary Response during Exercise in Children

The pulmonary response to exercise in children appears to differ from adults. Children respond to exercise and volitional exertion in a variety of ways based on growth and maturation-related development. According to Bar-Or and Rowland (2004), there are three different patterns of response to function–size relationships in the growing child. First, function is directly related to size; examples include muscle strength, VO_{2max}, maximal minute ventilation, and lung diffusing capacity. Second, function is related to qualitative changes and size, demonstrated by oxygen cost during exercise, anaerobic muscle power, and resting metabolic rate. Third, function is completely independent of body size, such as arterial O_2 content, serum electrolyte level, core body temperature, and rate of enzymatic action (Bar-Or and Rowland, 2004).

Pulmonary structure differences between children and adults are also apparent. Children have smaller airways relative to lung size than adults (Mead, 1980). Although there is a complex relationship between anthropometric measures and age in predicting

lung function, Kivastik and Kingisepp (1997) found similar growth patterns of thoracic dimension to lung function parameters in children. Among children that are normalized to height, regardless of sex, lung function differences can be partly attributed to differences in thoracic size. For other factors, specifically VO_2, differences in body size cannot directly account for the variability in oxygen uptake response to exercise. Complex relationships exist in children between anthropometric measures and response to exercise (Schwartz, 1988).

Aerobic Capacity

The exercising child exhibits differences in oxygen uptake compared to adults. Studies done in the early 1980's and 1990's confirmed faster VO_2 kinetics in children than adults (Freedson et al, 1981). About a decade later, Armon et al (1991) investigated the differences in oxygen uptake in children performing low and high intensity exercise. When children exercise at a high intensity, or above lactate threshold, oxygen transients are significantly faster than adults, whereas at low-intensity exercise, oxygen kinetics are independent of age and body size. Faster oxygen kinetics in children imply a smaller oxygen deficit at the start of intense exercise. Fawkner et al (2002) conducted a study with 25 adults (ages 19-26 years) and 23 children (ages 11-12 years) and concluded that children had significantly faster time constants than adults. A faster time constant may indicate a greater potential for oxidative metabolism in children.

Ventilation during Exercise

When controlled for body size, ventilation at rest and during submaximal exercise is higher in prepubescent children. Longitudinal data shows a decrease of 26% in

submaximal ventilation per kilogram of body mass from age 9 to 14 in girls and boys during treadmill exercise (Rowland et al, 1997). The difference between submaximal and maximal ventilation denotes ventilatory reserve, and increases with age, suggesting that children use a larger percentage of their ventilatory reserve until they reach adolescence.

Maximal ventilation is determined by breathing frequency and tidal volume. It is well known that exercising children have a higher breathing frequency than adults when performing similar tasks (Astrand, 1952; Gratas-Delamarche et al, 1993; Rowland et al, 1997; Nagano et al, 1998). Absolute ventilation increases with age; as respiratory frequency decreases with age, tidal volume increases in proportion to body mass (Mercier et al, 1991).

Like adults, children increase ventilation linearly until they reach ventilatory threshold at about 60-70% of VO_{2max}. Thereafter, ventilation rises in accelerated fashion in relation to the rise in oxygen uptake. This exaggerated ventilation is in response to metabolic acidosis and an increase in non-metabolic CO_2 evolution (Bar-Or and Rowland 2004; Rowland et al, 1997). Children may regulate their end tidal PCO_2 at a lower level than adolescents or adults, possibly due to growth-related changes in storing CO_2 in tissues (Nagano et al, 1998; Pianosi and Wolstein, 1996). A lower end tidal PCO_2 set-point during exercise could be accounted for by a higher metabolic rate in children, but it is more likely that respiratory control is dependent on maturational changes in the sensitivity of the central and peripheral chemoreceptors (Gratas-Delamarche et al, 1993).

By ventilating "out of proportion" to metabolic demands, the efficiency of breathing in children is questioned. The ventilatory equivalent (V_E/VCO_2) is a ratio used to express ventilatory efficiency; a high ratio suggests low efficiency. Ventilatory equivalent decreases with age (Andersen et al, 1974). Younger children seem to have

less ventilatory efficiency than older children or adults. Additionally, the depth of ventilation can be assessed from expressing the ratio of tidal volume to vital capacity. This ratio is slightly lower in children (Rutenfranz et al, 1981) as V_T/VC ranges from 0.42-0.48 in children and 0.56-0.59 in adults. Children do respond to exercise with relative tachypnea and more shallow breathing. The implications for less efficient ventilation can result in a greater cost of breathing and may limit exercise tolerance.

The consequence of increased ventilation in children, particularly an increase in breathing frequency, is likely an increase in dead space ventilation. The increased ventilatory response is, however, adequate to maintain PCO_2. Pianosi and Wolstein (1996) found that in children, a lower $PaCO_2$ was associated with a higher V_E/VCO_2 in steady state work, indicating that the magnitude of the ventilatory response to exercise is linked to $PaCO_2$.

The question is then do children breathe more in order to regulate $PaCO_2$ at a lower set point, or is their $PaCO_2$ lower because they breathe more? In either case, Pianosi and Wolstein (1996) suggested that together with a lower $PaCO_2$, a higher basal metabolic rate may also help to explain the greater ventilation in childhood.

Ventilatory Limitations during Exercise in Children

Compared to adults, normal, healthy children ventilate more relative to metabolic demand (Gratas-Delamarche et al, 1993; Cooper et al, 1987) and have smaller airways as a function of lung size (Mead, 1980). Because of children's breathe more rapid and shallow breathing, increased dead space ventilation, decreased efficiency of breathing,

they likely increase work of breathing due to more turbulent air flow. This type of breathing may cause children to adopt a specific breathing pattern that would cause them to reach ventilatory constraints during maximal exercise.

Expiratory Flow Limitation

Higher ventilation during exercise in children may lead to greater mechanical limits of ventilation at a lower relative VO_2 during exercise than in adults. Consequently, it is expected that children will also regulate their breathing in different patterns than adults during exercise. Nourry et al (2006) investigated ventilatory constraints in healthy, untrained, prepubescent children, measured by EFL relative to end-expiratory lung volume (EELV) and end-inspiratory lung volume (EILV). Ten out of 18 children demonstrated EFL ranging from 16-78% of tidal volume. Fifty percent of the subjects that demonstrated EFL experienced it at the beginning of exercise. This study indicates that EFL likely exists in children even if they do not present a high $VO_{2max,}$ whereas EFL is most commonly present in highly fit adult men and women. Typically, in adult men and women, EFL results in breathing at a high lung volume (increased EELV); however, EELV was not increased in children who demonstrated EFL in that study. Curiously, children who breathed at a higher lung volume at peak exercise were the ones who did not experience EFL. The difference could not be explained by age, height, body mass, fat percentage, BMI or FVC as there were no differences between groups. The authors explained this result as a higher V_{Epeak} in the children who were not flow limited, proposing that identifying tidal volume regulation is insufficient to estimate flow limitation in children. Based on the results of this study, children who experience

expiratory flow limitation regulate tidal volume differently than adults who experience expiratory flow limitation.

Effects of Training

Trained children who are able to reach high levels of VO_2 (Lussier and Buskirk, 1977) have increased V_E, and may therefore be more likely to experience ventilatory limitations. Ventilatory constraints were evaluated in trained (enrolled in aerobic sport activities lasting >5 hours/week) and untrained prepubescent boys and girls by plotting tidal flow volume loops during exercise inside the maximal flow volume loop at rest (Nourry et al, 2005). Important findings from this study have laid the groundwork for research in pulmonary responses in children during exercise. First, EFL was found in 9 of 13 trained children and in 8 of 11 untrained children. Second, trained subjects had significantly larger maximal flow volume loops and larger expiratory flows than untrained, indicating there may be a "fitness effect" found in trained children that leads to increased lung volume. Lastly, although there was similar prevalence of EFL in trained and untrained children, visual results of flow-volume loops and measures of EELV during exercise indicate different breathing patterns associated with children of varying fitness habits. EFL in trained children was accounted for by a greater ventilatory drive relative to a larger maximal flow-volume loop, whereas untrained children simply had smaller maximal flow-volume loops.

Untrained children have smaller maximal flow volume loops that cause them to reach mechanical constraints and consequently expiratory flow limitation during exercise (Nourry et al, 2005). Greater variability in regulation of EELV in untrained children is most likely a result of less ventilatory drive and no obligation to breathe in a specific pattern. Trained children have larger maximal flow volume loops, and a greater

ventilatory drive than untrained children, and more often experience EFL. Breathing strategies for the trained children consisted of an increased EELV and EILV. These increases move tidal volume to a higher lung volume resulting in a higher elastic load of breathing and an increased ventilatory drive. This study supports the hypothesis that trained children see greater ventilatory constraints than untrained children due to greater demand relative to lung capacity.

There are very few longitudinal training studies involving prepubescent children. However, Courteix et al (1997) reported that prepubescent girls can increase lung volume (VC, TLC, FRC) with swim training over the length of a year. What was not questioned until recently was the ability to similarly increase lung function with running training- the more habitual form of activity for children. Nourry et al (2005b) reported that after an 8 week, high-intensity running program with prepubescent children, there were also increases in lung function, specifically FVC, FEV_1, peak expiratory flows (PEF), and maximal expiratory flows (MEF) at rest. At submaximal work rates, trained children had a lower ventilatory response (V_E/VCO_2), indicating lower dead space ventilation relative to V_T during all exercise stages. At peak exercise, trained children had increased VO_2, V_E, and V_T. There seems to be an interaction between training and the maturation process of pulmonary structures allowing children to adapt to exercise demands.

Consequences of Expiratory Flow Limitation

Exercise-Induced Arterial Hypoxemia

Since children have smaller lung size and airway flows along with larger relative VO_{2max} values than adults (Rowland, 1996), children might also experience arterial oxygen desaturation during exercise. Arterial oxygen saturation was recently measured

during a graded exercise test until exhaustion in children by pulse oximetry in a study by Nourry et al (2004). EIAH was defined as a drop in oxygen saturation of > 4% from baseline and was present in seven of 24 subjects; the development of EIAH was significantly associated with lower FVC and breathing reserve in hypoxemic compared to non-hypoxemic subjects. Nourry et al (2004) stated that children who showed EIAH regulated $PaCO_2$ at a higher set point than non-hypoxemic children, but these results must be interpreted carefully because no difference in V_E, V_T, f, or $P_{ET}CO_2$ was found during exercise. The presence of EIAH in prepubescent children is a relatively new finding and more research is needed to better understand prevalence and mechanisms involved.

Dyspnea, Respiratory Muscle Fatigue, and Work of Breathing

Ventilatory limitations have consequences in healthy adults in the form of respiratory muscle fatigue, dyspnea, and work of breathing (see above). These are all contributing factors to the limitation of exercise tolerance in adults, but are not as well understood in normal, healthy children.

Dyspnea ratings in children are difficult to interpret and somewhat subjective, given the comprehension level of a child. Attempts have been made to create a technique in which the number of breaths are counted over 15 seconds (Prasad et al, 2000), however, most of the need for dyspnea ratings are used in children with respiratory diseases such as asthma and cystic fibrosis. Dyspnea has not been shown to limit exercise tolerance in healthy children with or without expiratory flow limitation (Nourry et al, 2006).

Numerous studies focus on peripheral muscle endurance in children, and results show no difference from normal, young adults (Rowland et al, 1990). However, it is difficult to predict similar respiratory muscle characteristics between children and adults.

Children have, surprisingly, shown high maximal respiratory pressures even compared to adolescents (Faroux, 2003), and this may be due to the mechanical properties of the thoracic cage and pulmonary system. Even though children seem to have relatively greater respiratory muscle strength at rest, they may not be able to sustain a given higher pressure for as long as adults. It was confirmed by Koechlin et al (2005) that reported respiratory muscle endurance was lower in prepubertal children compared to children near the end of the pubertal process. The underlying mechanisms of respiratory muscle fatigue are not yet known in children.

Work of breathing is not well documented in normal, exercising children. Techniques such as the measurement of esophageal pressure during exercise are not suitable for children, and the only studies that explore this phenomenon focus on severely diseased children that benefit from ventilator assistance. Because work of breathing depends on the pressure generated by the inspiratory muscles, it can be inferred that some children may experience increased work of breathing during exercise due to dynamic hyperinflation.

The consequences of ventilatory limitations during exercise in children need further study. Studies have demonstrated that children are receptive to training by inducing changes in resting pulmonary function and altered exercise ventilation. Nourry et al (2005b) reported slower and deeper ventilation after a high intensity training program, eliciting a more effective breathing strategy. Aerobic capacity is also increased through training, which may play a role in stimulating changes to respiratory muscles and the structural properties of the pulmonary system via the repetitive nature of training. Training studies in children help our understanding of pulmonary limitations and their consequences during exercise.

Sex Differences in Prepubescent Children

Sex differences during exercise in adults are generally associated with hormones, body composition (Wells, 2007), maximal oxygen uptake, and pulmonary function (McClaran et al, 1998). In prepubertal children, however, any sex differences that exist likely are not due to hormonal contributions because the onset of puberty is responsible for significant hormonal differences between boys and girls. Given the lack of pubertal hormones, hemoglobin concentration between sexes is similar in prepubescent children (Dallman and Siimes, 1979). In a study done by Armstrong et al (1995) with children ages 10 to 11, boys had significantly higher maximal aerobic capacity values than girls, but there were no differences in hemoglobin concentration. However, prepubescent boys and girls do differ in morphology/structure, aerobic capacity, and also pulmonary function.

Structural Differences

Prepubescent boys and girls generally have similar height and body mass, but this does not necessarily reflect properties of the lung. A complex relationship exists between sex, anthropometric measures and age in predicting lung function (Schwartz, 1988). Longitudinal studies demonstrate that the growth of the lung and thoracic dimensions lag behind standing height growth (Degroodt et al, 1986; Borsboom et al, 1993). Consequently, sitting height has been commonly used in replacement of standing height, as may be more closely associated with lung development (Kivastik and Kingisepp, 1997). Thoracic dimensions might also be useful measures of development of lung parameters (Degroodt et al, 1988). Kivastik and Kingisepp studied the difference in lung performance between boys and girls with reference to chest width, depth, and biacromial

diameter. The authors found very similar growth patterns of thoracic dimensions and lung function parameters, suggesting that differences in lung function between boys and girls of the same sitting height may be explained by differences in thoracic dimensions. While there are no differences in alveolar dimensions or number of alveoli per unit area or volume between girls and boys, boys typically have bigger lungs than girls (Thurlbeck, 1982). This results in greater total number of alveoli and larger alveolar surface area for similar statures in boys than girls.

Body composition in children is most accurately measured by DXA scan. This method requires little effort from subjects, and allows for highly reproducible measures. Body composition comparisons between preadolescent girls and boys present mixed results. In a study done by Rowland et al (2000), boys had significantly lower body fat than girls (n = 49), but no difference in lean body mass. Vinet et al (2003) reported significantly lower lean body mass in boys compared to girls (n = 35), but no difference in fat mass percentage. Dencker et al (2007) found significant differences between boys and girls (n= 246); boys had lower total body fat ($p = 0.008$) and higher lean body mass ($p < 0.001$). It is likely that results will vary widely with any given time period or demographic, but a recent research focus has been the effect of body composition on aerobic capacity.

Aerobic Capacity

Differences in aerobic capacity between sexes of prepubescent children have been reported (Bar-Or, 1983; Krahenbuhl et al, 1985). Collections of previous pediatric research indicate that VO_{2max} expressed relative to body mass is 15% higher in boys than girls at age 12 (Armstrong and Welsman, 1997). Boys have higher absolute VO_2, VO_{2max}

relative to body mass, lean body mass, and after allometric scaling compared to girls (Dencker et al, 2007).

It has been speculated that there are different cardiovascular functional responses between prepubescent girls and boys (Rowland et al, 2000; Vinet et al, 2003). Rowland et al (2000) studied the influence of cardiac functional capacity on maximal oxygen uptake in prepubertal boys and girls and found no difference in maximal heart rate or arterio-venous oxygen difference. Maximal stroke volume was measured by Doppler echocardiography and was found to be significantly higher in boys, but not after normalizing for body composition. Cardiac functional capacity, as well as body composition and size are responsible for difference in maximal oxygen uptake between boys and girls. When cardiac size was measured in prepubertal boys and girls, girls had smaller cardiac dimensions and left ventricular mass; however, cardiac size difference was mostly attributed to an overall smaller body size in girls (Vinet et al, 2003). When cardiac dimensions, stroke volume, and left ventricular mass were expressed relative to lean body mass, significant differences were eliminated between prepubertal boys and girls. Differences in cardiac functional size cannot be solely responsible for gender differences in maximal oxygen uptake, instead cardiac differences are just one reflection of overall less lean body mass in girls.

Pulmonary Responses to Exercise

Although boys have larger lungs than girls (Thurlbeck, 1982), lung function is not directly representative of this difference. It is well documented that lung volume is greater in boys compared to girls at rest (Wang et al, 1993; Armstrong et al, 1998; Gonzalez-Barcala et al, 2007). However, several studies document no difference

between genders in FEV_1 and mid-expiratory flows (MEF's) at rest, (Zapletal, 1982; Gonzalez- Barcala et al, 2007), while others do (Schwartz et al, 1988; Kivastik and Kingisepp, 1997; Armstrong et al, 1997).

During exercise, boys consistently have higher tidal volume and absolute ventilation when compared to girls (Rutenfranz et al, 1981; Armstrong et al, 1997). Higher ventilatory measurements are a direct reflection of higher peak VO_2 measures in boys. It is difficult to compare ventilation measurements between studies because they are primarily dependent on the exercise protocol (Armstrong et al, 1996), making inter-study comparisons difficult. Limitations during exercise have not been directly compared between prepubescent girls and boys, specifically with reference to expiratory flow limitation. Based on differences between structural capacity of the pulmonary system and demand placed on the body, there is reason to suspect sex differences in ventilatory limitations during exercise.

Summary

Pulmonary limitations exist during exercise in the form of gas exchange, respiratory muscle fatigue, and ventilatory constraints in highly fit men, older fit individuals and women. Of interest to this project is ventilatory constraints defined as expiratory flow limitation, which may be more prevalent in women. However, little is known about children's ventilatory response to exercise. It is not yet known if sex differences exist in prepubescent children regarding expiratory flow limitation during incremental exercise.

It was the purpose of this study, therefore, to determine the prevalence and implications of expiratory flow limitation during exercise in healthy prepubescent boys and girls. It was hypothesized that in prepubescent children, during heavy exercise: 1) expiratory flow limitation would be present in the majority of both boys and girls, 2) the degree of expiratory flow limitation would be greater in girls than boys due to smaller lungs in girls, 3) those subjects with the most expiratory flow limitation would show the greatest dynamic lung hyperinflation, and 4) those subjects with the most expiratory flow limitation would show the greatest exercise induced arterial desaturation.

CHAPTER 2 - METHODS

Forty healthy prepubescent children (20 girls, 20 boys) ages 7-11, were recruited in the community, and volunteered as subjects. All subjects were free of asthma or pulmonary disease, and demonstrated normal lung function as measured by standard pulmonary function tests (PFT's). All subjects showed a normal increase in their maximal flow volume envelope immediately following maximal exercise. Children were defined as first stage of maturation, as defined by Tanner stage 1 (Tanner, 1962). Subjects were characterized by physical activity habits via a physical activity questionnaire and categorized as competitively active (60 minutes per day of moderate intensity physical activity and participating a competitive sports team, boys, n = 12, girls, n = 8), recreationally active (60 minutes per day of moderate intensity physical activity, boys, n = 5, girls = 8), or sedentary (boys, n = 3, girls, n = 4). None of the subjects were involved in swim training. Each subject had a parent or guardian present to provide medical history information and informed consent. All research components were reviewed and approved by the Institutional Review Board of Human Subjects at Kansas State University, Manhattan, KS.

Experimental Design

Subjects reported to the lab on two separate occasions. A parent or guardian was present at both sessions. During session one, height and weight were recorded using a calibrated eye-level physical scale with height rod (Detecto, Webb City, MO). Subjects were then familiarized with a mouthpiece, and practiced performing maximal breathing

maneuvers. Standard pulmonary function measures were performed, following several practice trials, and consisted of lung diffusing capacity, lung volumes, maximal inspiratory and expiratory pressures, and maximal flow-volume loops. All tests were performed in triplicate. The subject then completed an incremental cycle ergometer test until exhaustion to determine maximal oxygen uptake (VO_{2max}). A second exercise test at constant work load (105% VO_{2max}) was performed to verify maximal oxygen uptake. During the second visit, each subject underwent a DXA (Dual-Energy X-Ray Absorptiometry) scan to determine body composition.

Tests and Measurements

Pre-Exercise Pulmonary Function Tests

Lung diffusing capacity (DLCO), total lung capacity (TLC), residual volume (RV), maximal inspiratory pressure (P_{Imax}) maximal expiratory pressure (P_{Emax}), and maximal flow-volume loops (MFVL) were assessed prior to exercise testing (SensorMedics 229 Metabolic Cart, SensorMedics Corp, Yorba Linda, CA). Diffusing capacity of the lung was measured from normalized alveolar volume ($DLCO/V_A$) prior to exercise using a test gas mixture of 0.3% acetylene, 0.3% carbon monoxide, 0.3% methane, 21% O2, with balance of N_2 using the intra-breath exhalation technique. TLC and RV were determined using the nitrogen wash-out technique. P_{Imax} was measured at RV, and P_{Emax} was measured at TLC. All tests were performed in triplicate or until values were within 10% of each other. The average value was used in analysis.

Maximal Aerobic Capacity (VO2max)

An incremental exercise test to exhaustion was performed using a cycle ergometer (Ergometer 800S, Sensor Medics Corp., Yorba Linda, CA) to determine VO_2max. Subjects were given consistent and complete instructions explaining the protocol of the test to ensure maximal volitional effort. Prior to testing, a 3-L calibration syringe was used to calibrate the flow sensor. Known gas concentrations that spanned the range of expected measurements were used to calibrate gas analyzers. Resting metabolic measurements were taken for three minutes. Subjects then began with a warm-up for approximately two minutes at a work rate of 20 watts, pedaling between 50-60 revolutions per minute (rev/min). Subjects were instructed to maintain this pedaling speed while the work rate was increased by 10 watts per exercise stage, and each stage lasted 90 seconds. Subjects remained seated throughout the test. After the warm-up period and following each minute of an exercise stage, subjects reported a rate of perceived exertion (RPE) and dyspnea value based on the modified Borg scale. Heart rate (HR) was monitored throughout the test via a four lead ECG interfaced to the metabolic software. A pulse oximeter (Datex-Ohmeda, 3900P, Madison, WI) was secured to the left earlobe to estimate arterial oxygen saturation (SaO_2). The pulse oximeter was calibrated before each test. The pulse oximeter supplied a visual pulse waveform to ensure adequate blood perfusion. Values were averaged over the last minute of each stage. Subjects continued to exercise until reaching volitional exhaustion (< 16 minutes). Verbal encouragement was provided throughout the test. The VO_{2max} test concluded when subjects could not maintain a pedal frequency of 50 rev/min for five consecutive revolutions. Metabolic and ventilatory data were assessed continuously

through breath-by-breath analysis (SensorMedics 229 Metabolic Cart, SensorMedicsCorp., Yorba Linda, CA).

Following VO_{2max} test completion, subjects rested for 15 minutes and then performed a constant load exercise test until exhaustion to verify VO_{2max} (Poole et al, 2008). Work rate for the test was determined by 105% of their final work rate (watts) during the incremental test. Subjects were given a warm-up period of 90 seconds pedaling 50 rev/min at 20 watts. Work rate was increased until reaching calculated work rate (~30 seconds) and subjects were instructed to maintain 50 rev/min until volitional fatigue.

Expiratory Flow Limitation and Tidal Volume Regulation

Expiratory flow limitation (EFL) was determined by recording tidal volume loops during incremental exercise using a bidirectional flow sensor together with the gas analyzer. The exercising tidal volume loops were placed within the maximal flow volume envelopes (Johnson et al, 1999) that were determined post-exercise. At the end of each exercise stage, following 5-10 tidal breaths, an inspiratory capacity (IC) maneuver was performed from functional residual capacity (FRC). Subjects were familiarized with performing inspiratory maneuvers and were given the opportunity to practice prior to the start of exercise. The flow signal automatically corrected for any drift, assuming the volume of inspired and expired breaths were the same as resting breaths (Koulouris et al, 1995). EFL was defined as present when the intersection of the exercising tidal volume loop and the maximal flow volume loop was 5% or greater (Chapman et al, 1998; Nourry et al, 2006). The change in regulation of tidal volume

within FVC during exercise was recorded as end-expiratory lung volume (EELV) and end-inspiratory lung volume (EILV). EELV and EILV were expressed as ratios of expiratory reserve and inspiratory reserve volume relative to FVC (ERV/FVC, IRV/FVC). During analysis, approximately five breaths prior to the inspiratory capacity maneuver during exercise were monitored to track any changes in breathing regulation or flow sensor drift.

Body Composition

Total body composition was measured by use of a whole body DXA system (v5.6, GE Lunar Corp., Milwaukee, WI). Subjects lay in a supine position with arms separated from trunk and legs slightly spaced apart. Shoes and metal objects were removed prior to scanning. Instructions were to lie as still as possible during the scanning procedure. DXA scanning has been validated and uses two x-ray beams with differing energy levels to find differences in absorption and therefore lean body mass (LBM), body fat percentage, and body fat distribution (Haarbo et al, 1991).

Statistical Analysis

SigmaStat statistical software (Janel Scientific Software) was used for data analysis. Data is expressed as mean $\pm$ standard deviation. Differences between sexes were determined using ANOVA. Relationships were determined by Pearson Product Moment Correlation. Significance was set at $p < 0.05$ for all analyses.

CHAPTER 3 - RESULTS

Subject characteristics are presented in Table 1. The male to female ratio was equal (n = 20 girls, n =20 boys). No significant differences were found in anthropometric data or body composition between boys and girls ($p > 0.05$). None of the children had been diagnosed with asthma by a physician and no subjects demonstrated exercise induced asthma, as defined by a drop in FEV_1 pre to post exercise by >10%. Medical history information provided by a parent or guardian confirmed that all subjects were in Tanner maturation stage 1 (Tanner, 1962).

Table 1.Subject Characteristics

	Boys (n=20)		**Girls (n=20)**	
	mean ± SD	range	mean ± SD	range
Age (yr)	9.8± 0.6	8.2 - 11.0	9.5 ± 0.9	7.6 - 11.4
Weight (kg)	34.3 ± 7.8	26.0 - 55.6	32.9 ± 12.2	24.8 – 78.2
Height (cm)	140.0 ± 5.5	132.1 - 149.9	136.3 ± 7.2	125.7 - 151.1
Lean Body Mass (%)	77.3 ± 9.5	57.3 - 88.4	74.5 ± 9.9	48.4 - 87.5
Body Fat (%)	19.6 ± 10.4	7.9 - 42.8	22.7 ± 10.5	9.1 - 50.5
BSA (cm^2)	1382.4 ± 165.0	1139 - 1708	1271.2 ± 197.6	1038 - 1769
BMI (kg/m^2)	17.5 ± 3.7	21.1 - 27	17.4 ± 4.7	13.9 – 34.2

No significant differences between groups ($p > 0.05$)

Metabolic and Ventilatory Data

Resting Pulmonary Function

Table 2 displays baseline lung volumes and resting pulmonary function. Baseline PFT's were not significantly different from predicted values for prepubescent children (Knudson et al, 1983). All variables were significantly higher in boys than girls, with the exception of the ratio FEV_1/FVC.

Table 2.Resting Pulmonary Function

	Boys (n=20)		**Girls (n=20)**	
	mean ± SD	range	mean ± SD	range
TLC (L)	2.6± 0.5*	1.9 - 3.5	2.1 ± 0.5	1.4 - 2.9
FVC (L/sec)	2.2 ± 0.3*	1.7 - 2.9	1.9 ± 0.4	1.4 - 2.8
RV (L)	0.4 ± 0.3*	0.1 - 1.2	0.2 ± 0.2	0.1 - 0.7
FRC (L)	0.9 ± 0.3*	0.4 - 1.9	0.7 ± 0.3	0.2 - 1.3
DLCO (mmHg/L/min)	15.9 ± 3.0*	11.7 - 23.8	12.1 ± 3.2	7.6 - 20.1
PEF (L/sec)	3.6 ± 0.7*	2.3 - 4.8	2.9 ± 0.6	1.8 - 4.3
FEV_1 (L/sec)	1.9 ± 0.2*	1.6 - 2.5	1.6 ± 0.3	1.3 - 2.4
FEV_1/FVC (%)	85.3 ± 6.5	76 - 96	82.4 ± 6.9	64 – 89
$FEF_{50\%}$ (L/sec)	2.3 ± 0.5*	1.3 - 3.1	1.9 ± 0.5	1.0 - 3.0
$FEF_{25-75\%}$ (L/sec)	2.1 ± 0.4*	1.4 - 2.8	1.7 ± 0.4	0.8 - 2.7
P_{Imax} (cm H_2O)	83.7 ± 25.9*	33 - 125	72.1 ± 24.9	28 – 119
P_{Emax} (cmH_2O)	72.9 ± 17.4*	43 - 119	64.8 ± 20.5	32 – 110

FVC, forced vital capacity; PEF, peak expiratory flow; FEV_1, forced expiratory volume in 1 sec; $FEF_{50\%}$, forced expiratory flow at 50%; $FEF_{25-75\%}$, forced expiratory flow between 25-75%, P_{Imax}, maximal inspiratory pressure; P_{Emax}, maximal expiratory pressure; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; DLCO, lung diffusing capacity.

*** Significantly higher than girls ($p<0.05$)**

Exercise Data

Data collected during exercise and at VO_{2max} is shown in Table 3. There were no differences ($p>0.05$) between sexes in any measured variable during rest or submaximal exercise. There was also no difference in VO_{2max} between the incremental test (boys = 34.1 $\pm$ 8.3 ml/kg/min, girls = 29.5 $\pm$ 6.6 ml/kg/min) and constant load test at 105% VO_{2max} (boys = 33.2 $\pm$ 8.3 ml/kg/min, girls = 27.9 $\pm$ 6.1 ml/kg/min). However, at VO_{2max}, V_E, VCO_2, and work rate were significantly higher in boys when compared to girls. There were no significant differences in V_T, breathing frequency, or ventilatory equivalents (V_E/VO_2, V_E/VCO_2), HR, or RER between boys and girls. Oxygen saturation (SaO_2) was maintained within 3% of resting values in all subjects throughout exercise and was not different between boys and girls.

Expiratory Flow Limitation (EFL)

Prevalence

Table 4 shows prevalence and amount of EFL at VO_{2max}. In agreement with our first hypothesis, EFL was present in 19 of 20 boys (95%) and 18 of 20 girls (90%) at VO_{2max}. Figure 1 shows the degree of EFL in boys and girls from rest throughout exercise expressed in absolute and relative VO_{2max} values. Substantial increases in EFL were observed in both sexes at VO_2 of ~20-30 ml/kg/min or 60-80% VO_{2max}. There were no significant differences between boys and girls at any given VO_2 or percent of VO_{2max} during exercise. Contrary to our second hypothesis, there was no difference ($p>0.05$) in severity of EFL between boys and girls.

Table 3.Ventilatory and Metabolic Data during Exercise

	40%VO_{2max} *mean + SD*	60%VO_{2max} *mean + SD*	80% VO_{2max} *mean + SD*	VO_{2max} *mean + SD*	*range*
VO_2 (ml/kg/min)					
boys	14.5 ± 2.7	21.6 ± 4.2	28.3 ± 5.9	35.4 ± 7.5*	20.7 - 47.3
girls	12.3 ± 2.4	18.2 ± 4.4	24 ± 5.7	29.5 ± 6.6	17.4 - 39.8
VO_2 (ml/kg LBM/min)					
boys	19.3 ± 2.8	28.7 ± 3.4	37.4 ± 4.9	46.9 ± 5.9*	36.3 - 59.3
girls	17.9 ± 2.9	26.2 ± 4.7	33.3 ± 5.6	41.7 ± 6.6	26 - 52.2
VO_2 (l/min)					
boys	0.5 ± 0.1	0.7 ± 0.1	1.0 ± 0.1	1.2 ± 0.2*	0.9 - 1.5
girls	0.4 ± 0.1	0.6 ± 0.1	0.8 ± 0.2	0.9 ± 0.2	0.6 - 1.4
V_E (l/min)					
boys	18.2 ± 3.6	25.8 ± 3.5	35.7 ± 4.2	49.8 ± 8.8*	32.7 - 69.9
girls	16.3 ± 2.7	23.8 ± 4.4	32.6 ± 6.6	41.2 ± 8.3	26.3 - 52.7
V_T (l)					
boys	0.6 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.7 - 1.3
girls	0.6 ± 0.1	0.7 ± 0.1	0.7 + 0.2	0.8 ± 0.2	0.5 - 1.4
Fb (breaths/min)					
boys	30.3 ± 7.8	36.1 ± 6.9	45.4 ± 6.4	57.6 ± 12.3	26 - 76
girls	31.1 ± 6.2	37.9 ± 9.3	46.8 ± 11.5	53.5 ± 13.1	34 - 88
VCO_2 (l/min)					
boys	0.4 ± 0.1	0.7 ± 0.1	0.9 ± 0.2	1.2 ± 0.2*	0.9 - 1.6
girls	0.3 ± 0.1	0.5 ± 0.1	0.8 ± 0.2	0.9 ± 0.2	0.5 - 1.5
V_E/VCO_2					
boys	44.1 ± 9.8	40.9 ± 8.2	39.6 ± 4.0	41.1 ± 3.9	34 - 49
girls	51.2 ± 8.7	45.6 ± 8.8	44.4 ± 6.2	43.4 ± 5.5	34 - 53
V_E/VO_2					
boys	40.9 ± 12.0	38.7 ± 9.3	38.1 ± 4.2	41.3 ± 4.2	33 - 50
girls	45.9 ± 9.2	45.3 ± 12.5	43.7 ± 7.7	43.4 ± 5.9	28 - 52
$P_{ET}O_2$ (mmHg)					
boys	99.2 ± 4.9	100.9 ± 3.2	104.8 ± 3.1	109.7 ± 3.6	100.3 - 115.0
girls	101.2 ± 4.0	104.4 ± 3.7	107.5 ± 3.3	109.8 ± 4.9	92.8 - 114.2
$P_{ET}CO_2$ (mmHg)					
boys	39.1 ± 3.7	39.2 ± 3.1	38.2 ± 2.6	35.5 ± 2.5	31.6 - 40.7
girls	37.4 ± 2.7	37.5 ± 2.7	36.5 ± 2.8	35.7 ± 3.2	31.2 - 44.5
HR (bpm)					
boys	121.2 ± 12.3	138.8 ± 13.8	158.0 ± 17.1	174.4 ± 23.1	123 - 204
girls	125.4 ± 12.5	149.5 ± 16.7	172.2 ± 14.2	183.4 ± 16.6	147 - 205
SaO_2 (%)					
boys	98.9 ± 0.9	98.3 ± 1.3	97.9 ± 1.6	96.7 ± 3.4	94 - 99
girls	99.5 ± 0.6	98.9 ± 0.8	98.2 ± 1.5	97.7 ± 1.3	95 – 99
RER					
boys	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	0.9 - 1.1
girls	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.8 - 1.1
Work (watts)					
boys	30.5 ± 8.9	53.0 ± 11.7	75.0 ± 12.4	97.5 ± 15.2*	60 - 120
girls	25.0 ± 5.9	46.5 ± 9.9	65.0 ± 11.5	80.5 ± 18.1	50 - 110

VO_2, oxygen uptake; V_E, minute ventilation; V_T, tidal volume; VCO_2, carbon dioxide output; $P_{ET}CO_2$, end tidal partial pressure carbon dioxide; SaO_2, arterial oxygen saturation (boys, n = 20; girls, n = 20)

***Significantly different from girls ($p<0.05$)**

We were interested in determining if the amount of EFL was related to V_{Emax}, VO_{2max}, or total lung volume. Figure 2 shows V_{Emax} and % EFL at VO_{2max}. There was no relationship ($p>0.05$) between these variables. Further, groups of boys and girls were each divided by the 50^{th} percentile based on VO_{2max} (Fig 3A) and TLC (Fig 3B). There were no significant differences between subjects with low VO_{2max} (boys = 29.6 ml/kg/min, girls = 24.3 ml/kg/min) and high VO_{2max} (boys = 41.3 ml/kg/min, girls = 34.7 ml/kg/min). There was no relationship ($p>0.05$) between VO_{2max} and % EFL at VO_{2max} ($r = 0.21$). There were also no significant differences between boys and girls with low TLC (boys = 2.2L, girls = 1.7L) and high TLC (boys = 2.9L, girls = 2.6L). There was no relationship ($p>0.05$) between TLC and % EFL at VO_{2max} ($r = 0.24$).

Regulation of Tidal Volumes

Individual and mean changes in EELV, as reflected by ERV/FVC from rest to exercise in boys and girls are represented in Figure 4. Twelve of 20 boys and 18 of 20 girls increased ERV/FVC from rest to $VO_{2max.}$ There was a significant increase in ERV/FVC with the average increase of 21.3 $\pm$ 4.9 % in boys and 25.6 $\pm$ 3.4 % in girls. Figure 5 shows the relationship between % EFL at VO_{2max} and the change in ERV/FVC from rest to maximal exercise in boys (A) and girls (B). In agreement with hypothesis 3, those subjects who experienced flow limitation also demonstrated the greatest increase in ERV/FVC. There was a significant relationship between these variables in both boys ($r = 0.77$) and girls ($r = 0.75$), indicating that those subjects with the greatest severity of EFL at VO_{2max} had the greatest increase in end expiratory lung volume (dynamic hyperinflation) at $VO_{2max.}$ Finally, because there was no significant arterial desaturation

in any subjects, our data contradicts the hypothesis that the greatest degree of EFL would be associated with the most severe arterial oxygen desaturation.

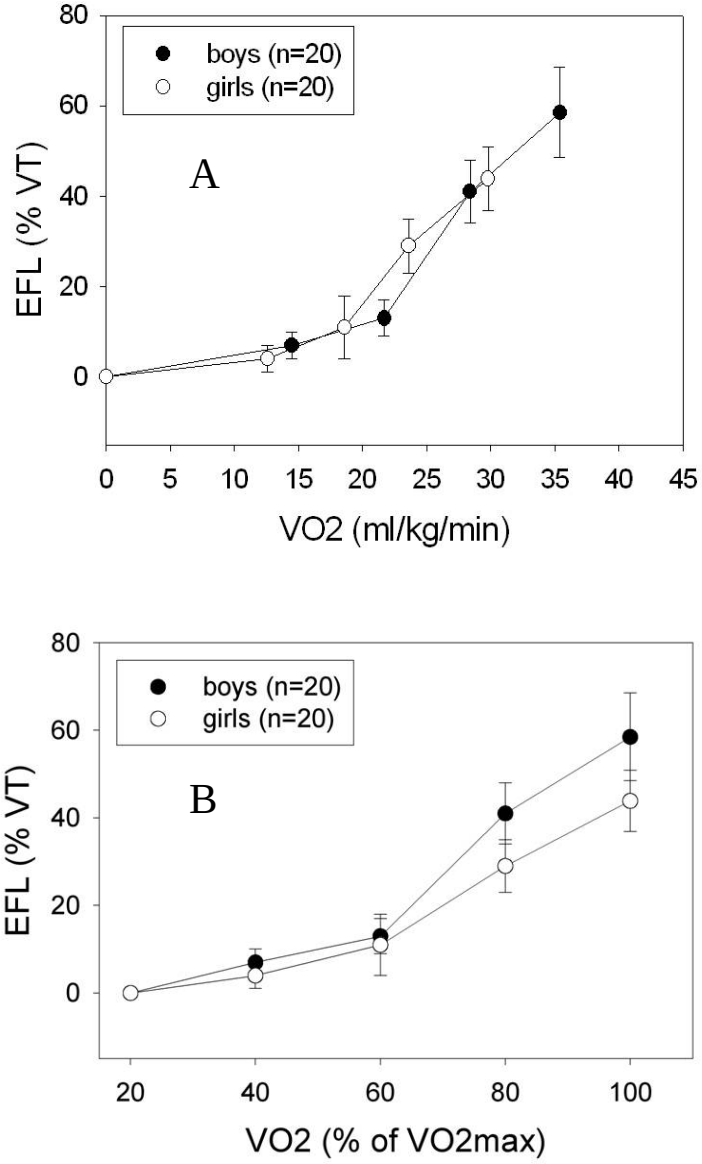

Figure 1. Degree of EFL in boys and girls during exercise expressed in absolute (A) and relative (B) values. There were no differences between sexes at any exercise intensity in EFL.

Table 4. Expiratory Flow Limitation

	Boys	Girls
Prevalence of EFL	19/20	18/20
EFL (% V_T) at VO_{2max}	58 ± 7	43 ± 8

There are no significant differences between groups (p>0.05)

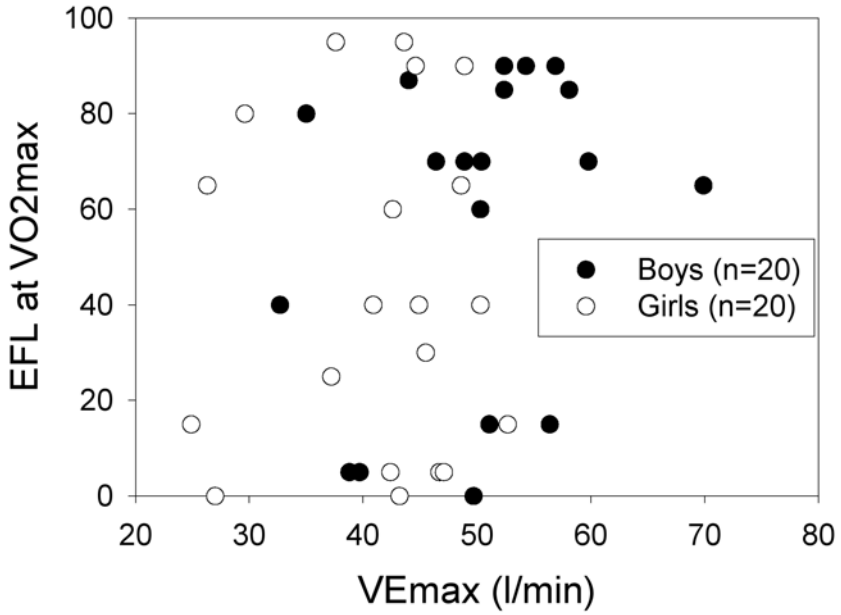

Figure 2. Relationship between maximal ventilation and EFL at VO_{2max}. There is no correlation between V_{Emax} and EFL at VO_{2max}.

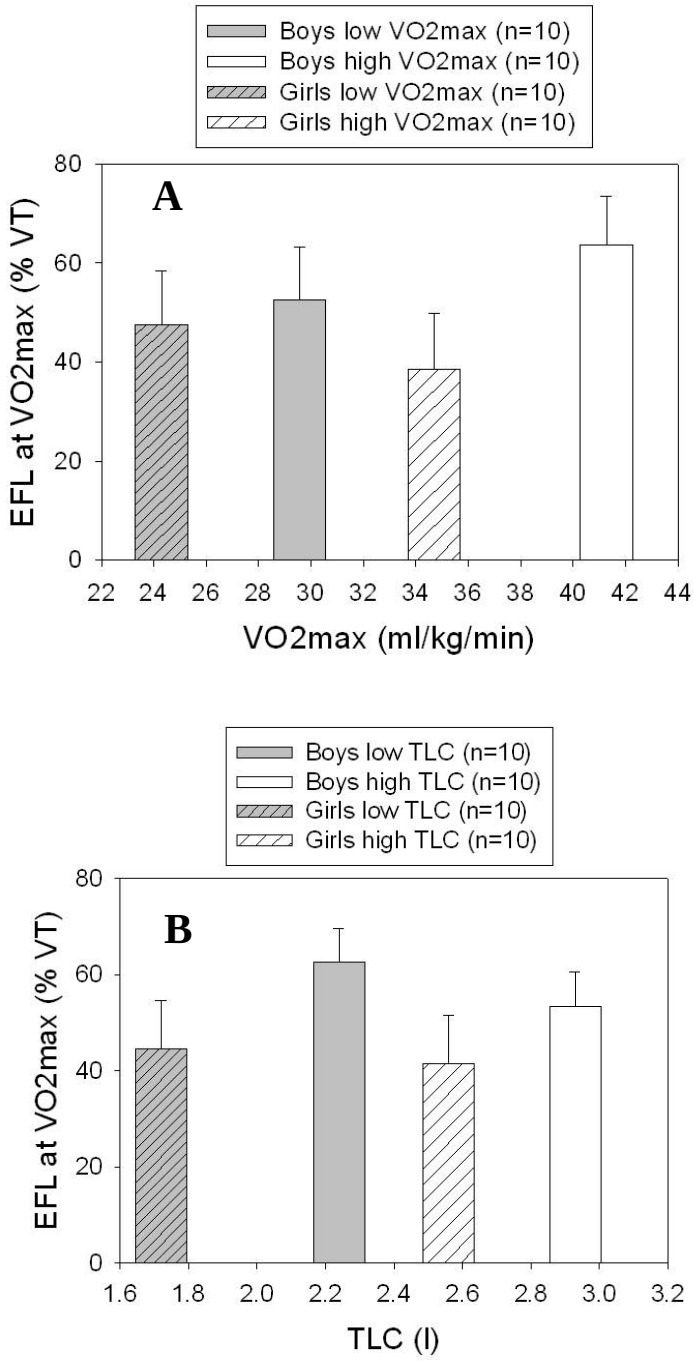

Figure 3. Expiratory flow limitation vs VO_{2max} (A) and TLC (B).No difference (P>0.05) between groups in the amount of of % EFL at VO_{2max} relative to aerobic capacity (VO_{2max}) or lung volume (TLC). There was also no relationship (p>0.05) between these variables.

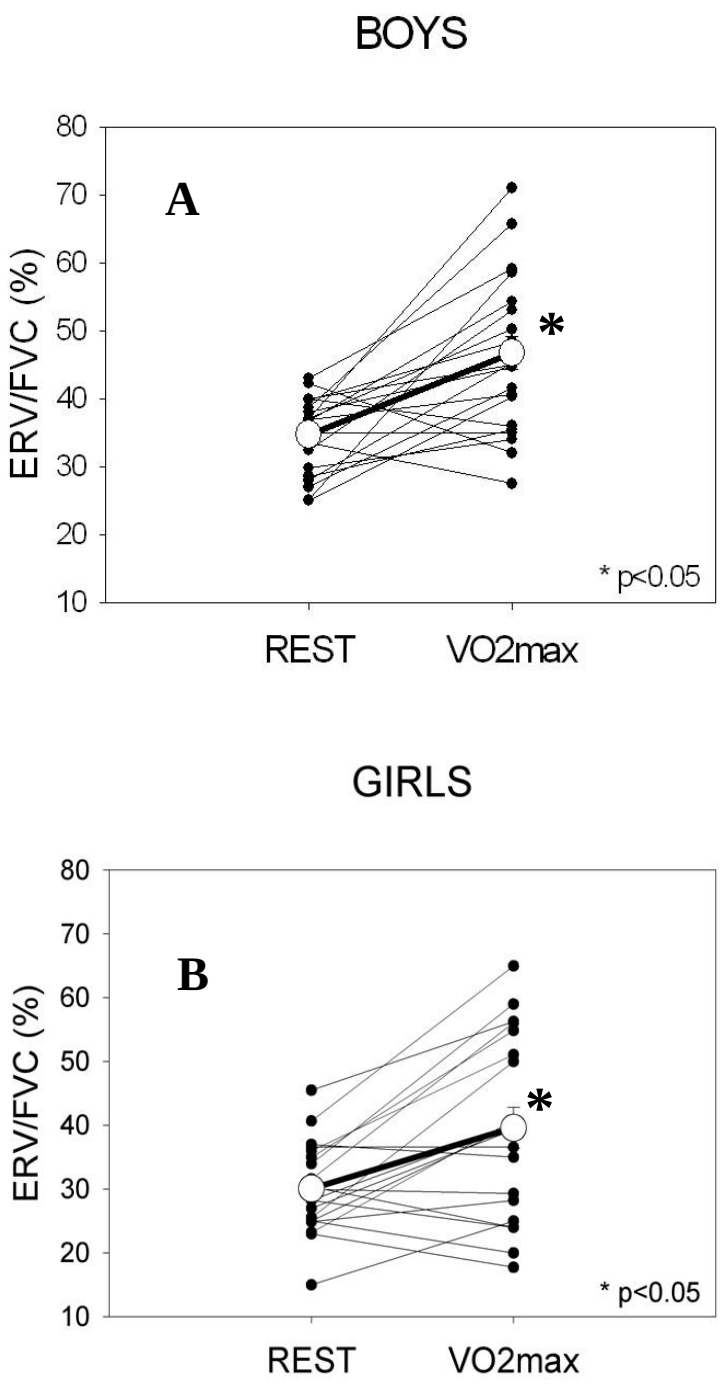

Figure 4. Individual and mean change in ERV/FVC from rest to VO_{2max} in boys (A) and girls (B). Significant increases occurred from rest to VO_{2max} in %ERV/FVC in both boys and girls.

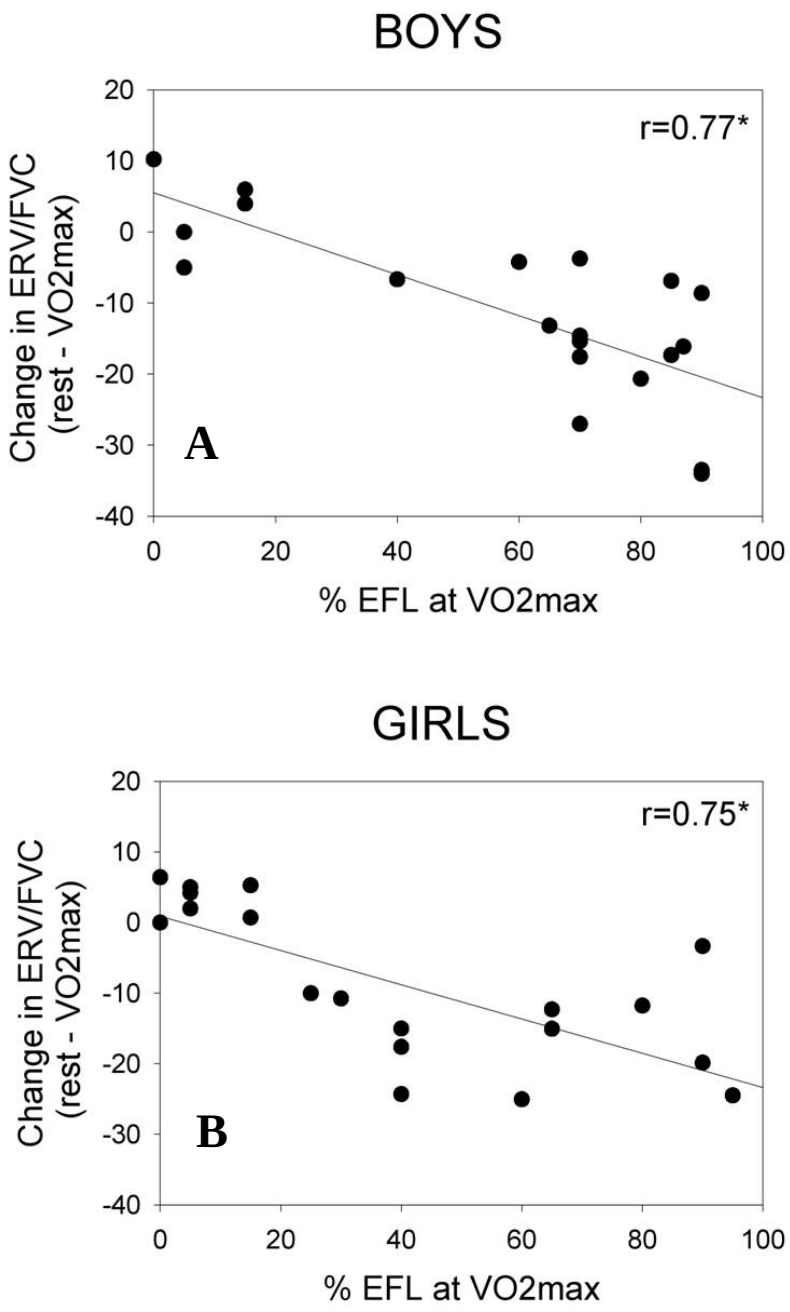

Figure 5.Relationship between the change in ERV/FVC from rest to VO_{2max} to expiratory flowlimitation in boys (A) and girls (B). Of the boys and girls who demonstrated EFL, the subjects who exhibited the most EFL had the largest increase in end-expiratory lung volume (dynamic hyperinflation) during exercise. * p < 0.05

CHAPTER 4 - DISCUSSION

Major Findings

The purpose of this study was to determine the prevalence and implications of expiratory flow limitation (EFL) during exercise in healthy, prepubescent children. Our major findings support our first hypothesis that EFL would be present in the majority of prepubescent boys and girls during heavy exercise which would lead to increased end expiratory lung volume. However, contrary to hypothesis 2, we were surprised with the extremely high prevalence of EFL in both boys and girls. We have also shown, for the first time, that there was no difference in prevalence of EFL between sexes. Similar prevalence of EFL occurred despite boys having larger lungs and aerobic capacity than girls even when matched for height, weight, and body composition. In agreement with hypothesis 3, the subjects with the greatest EFL also indicated the greatest dynamic hyperinflation. Our results also indicated that EFL during exercise could not be predicted based on aerobic capacity, exercise ventilation, or total lung capacity. Lastly, in spite of the high prevalence of EFL, and contrary to hypothesis 4, there was minimal arterial oxygen desaturation throughout exercise even in those subjects with the greatest EFL.

Prevalence of Expiratory Flow Limitation

The high prevalence of EFL in our subjects is consistent with previous literature that reports significant EFL in trained (Nourry et al, 2005) and untrained prepubescent children (Nourry et al, 2006). Nourry et al (2005) studied 24 children (11 untrained, 13 trained) to determine EFL and tidal volume regulation. Results indicated that trained

children breathed at a higher lung volume during exercise, yet the proportion of trained and untrained children who experienced EFL (8 of 11 untrained, 9 of 13 trained) was not significantly different. In 2006, Nourry et al conducted a study that evaluated breathing patterns and flow-volume loops to analyze ventilatory constraints in 18 healthy, untrained prepubescent children. EFL occurred in 10 of 18 subjects. Flow-limited subjects regulated breathing in dissimilar patterns compared to non-flow-limited children, and there was no association of EFL with age, size, body mass, fat mass percentage, or body mass index (BMI). We found similar results even when we included girls and subjects with wider ranges of aerobic capacities and body composition in our research design.

Certain adult populations experience EFL during exercise, including highly fit individuals, older adults, and pulmonary disease patients, primarily due to a conflict between capacity of the pulmonary system and metabolic demands of exercise (Johnson et al, 1991; McClaran et al, 1998; Johnson et al, 1999; Babb et al, 1999). Several differences in ventilatory response to exercise exist between children and adults that may explain the higher prevalence of EFL in children. First, children have smaller airways relative to lung size compared to adults (Mead, 1980). The ratio of airway size (maximal expiratory flow divided by static pressure at 50% of vital capacity) to lung size (vital capacity) was reported higher in men than in women or children (Mead, 1980). For adult males, airway diameter was independent of lung size, but airway length was dependent on lung size. However, for women and children, the ratio was smaller indicating that the airways are smaller relative to lung size.

Second, children ventilate out of proportion to metabolic demand during heavy exercise (Cooper et al, 1987; Gratas-Delamarche, 1993). It has been well documented that ventilation in children is higher than adults at rest (Levison et al, 1970; Jammes et al,

1979) and during exercise (Astrand, 1952; Andersen et al, 1974; Gratas et al, 1986). Arterial blood gas tensions do not differ in adults and children (Gadhoke and Jones, 1969), so the difference in ventilation at rest and during exercise is likely due to a mixture of morphological, metabolic and central nervous system factors that dictate a higher V_E is required to regulate $PaCO_2$ ~ 40mmHg (Gratas-Delamarche et al, 1993). Morphological factors, such as the mechanical limitation of tidal volume due to smaller lungs may affect the breathing pattern in children (Gaultier and Girard, 1980). The more shallow breathing does not allow efficient alveolar air wash out, and the higher respiratory frequency leads to greater total mechanical work of breathing in children compared to adults. These two factors cause children to ventilate more than adults for a similar metabolic demand expressed per unit of body mass.

An increased response to CO_2 during exercise is a central nervous system factor that may also contribute to higher ventilation per unit metabolic rate during exercise. Gratas-Delamarche (1993) confirmed the importance of CO_2 responsiveness in children's respiratory centers. Results showed differences in ventilation at a given end tidal PCO_2 between adults and children during exercise; children demonstrated a lower sensitivity threshold, a higher reactivity slope, and a greater mean inspiratory flow, indicating a greater ventilatory response to CO_2. Our data support this premise. Compared to adults (West, 2008), our subjects demonstrated significantly higher ventilatory equivalent for O_2 and CO_2, a reflection of "excessive" ventilation relative to exercise demand. However, ventilation appears sufficient, as arterial PCO_2 is maintained in children, (Gratas-Delamarche et al, 1993) despite the probable increase in dead space ventilation. Even though the breathing pattern is not as efficient in children, arterial PCO_2 is held at its resting level. It seems that the increase in ventilatory response to CO_2 is likely due to

central nervous system factors. The higher ventilatory equivalent combined with smaller lung volumes than adults in our study indicate children's increased susceptibility to ventilatory constraints in the form of EFL during exercise.

Sex Differences in EFL during Exercise

McClaran et al (1998) and Guenette et al (2007) reported that women experience a significant amount of EFL during heavy exercise, primarily due to smaller lung size and lower peak expiratory flow rates than men. These studies indicate adult women use a larger percentage of ventilatory reserve during exercise than men. To our knowledge, there have been no previous reports which have directly compared EFL during exercise between prepubescent boys and girls. Prepubescent boys have larger lungs (Thurlbeck, 1982) and larger lung volumes at rest (Wang et al, 1993; Armstrong et al, 1998) than girls. Also consistent with adults, boys have greater ventilation and tidal volume measures (Rutenfranz, 1981; Armstrong et al, 1997) compared to prepubescent girls. Given that girls have smaller lungs relative to body size and lower ventilation during exercise, we predicted that EFL would be greater in girls. We were surprised to find the prevalence and severity of EFL during exercise similar between boys and girls. Our data does suggest, however, that the balance between metabolic demand and pulmonary capacity in determining EFL is different between boys and girls.

Sex differences in pulmonary function in prepubescent children cannot be attributed solely to anthropometric differences, but there are several hypotheses that attempt to explain pulmonary function differences in children. The rationale for sex differences in dynamic lung volumes are not yet defined, however, there is data to

suggest that mechanical properties of the lung are different between boys and girls (Taussig et al, 1981). Further, Wang et al (1993) suggested that sex differences in lung function are more complex than dynamic growth of the airways and include differences in ventilation-perfusion homogeneity between girls and boys.

Based on previous reports, we predicted that boys would have larger lung volumes and greater aerobic capacity than girls. Regarding aerobic capacity, our results show that boys had greater VO_{2max} values than girls, even when normalized for lean body mass. Previous studies (Astrand, 1952; Andersen et al, 1952; Rutenfranz et al, 1981) have shown when scaled for LBM, the sex difference in VO_{2max} lessens. Rowland et al (2000) found a 12% difference between boys and girls in absolute VO_2, and a 2% sex difference when VO_{2max} was scaled to LBM. Similarly, in a larger study of 248 children (Dencker et al, 2007), the absolute value difference in VO_{2max} between boys and girls was 18%, but decreased to 8% when scaled for LBM. Given the increased ventilatory demand associated with increased VO_2, we predicted that the severity of EFL would be positively associated with VO_{2max} or VO_{2max}/LBM. However, our data found no relationship between either variable. In agreement with this finding, previous studies have also shown that EFL does not seem to be related to aerobic capacity in children (Nourry et al, 2006).

Prepubescent boys have higher V_E , V_T , and VO_{2max} compared to girls. Although highly dependent on exercise protocol, the greater VO_{2max} in boys likely drives the greater V_{Emax} in boys (Rutenfranz, 1981; Armstrong, 1997). Because boys have larger lung capacity, they may be able to generate higher ventilation levels than girls without experiencing ventilatory constraints. However, we found no relationship between V_E, lung capacity (TLC) and the amount of EFL in either boys or girls, suggesting that

different mechanisms underlie the similar prevalence rates of EFL in prepubescent children.

In summary, Figure 6 shows mean data from our subjects depicting the similarity in the amount of EFL in boys and girls. Notice the difference in how EFL is experienced. Specifically, in age and body-size matched boys and girls, girls experience EFL primarily due to smaller maximal flow-volume loop (MFVL) compared to boys. Significantly smaller lung volumes and maximal expiratory flows cause girls to be more susceptible to mechanical constraints of ventilation. Conversely, boys demonstrate a much larger MFVL than girls, but experience EFL primarily due to higher metabolic demand (VO_{2max}).

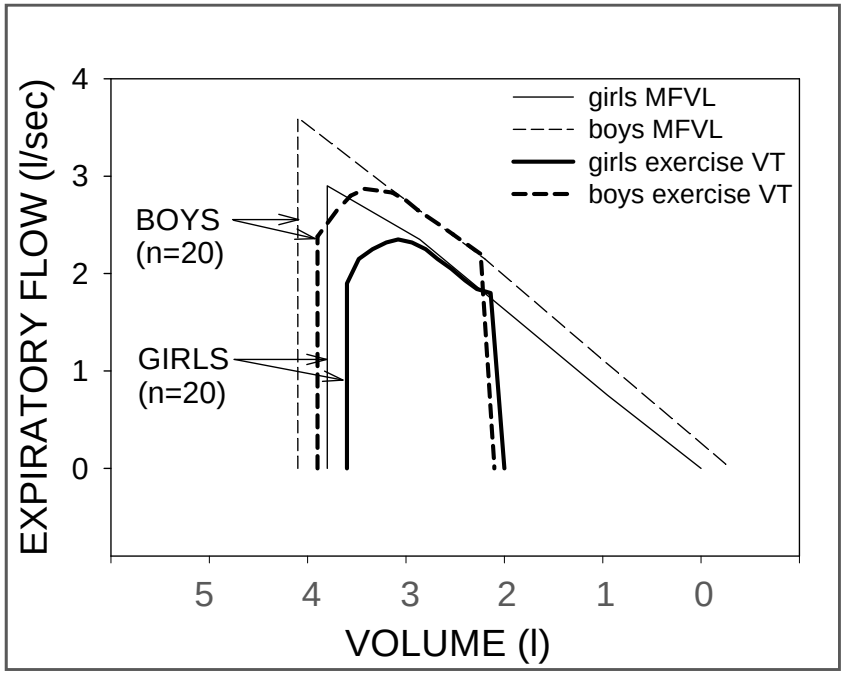

Figure 6. Summary of maximal flow-volume loops and exercising tidal volume loops for boys and girls.

Regulation of Tidal Volume during Exercise

Initially, it was reported that there were no differences in the regulation of lung volumes between adult men and women when normalized for FVC (Vogiatzis et al, 2005). Guenette et al (2007) noted that while there were no differences in breathing regulation during submaximal exercise between men and women, at maximal exercise the women had significantly higher EELV when normalized to FVC. Highly fit men and women who reach very high levels of ventilation during maximal exercise were used in this study, which may or may not have affected the amount of EFL that was present. Just as there was no difference in the amount of EFL between boys and girls in our study, there was also no difference in the regulation of tidal volumes in boys and girls from rest to maximal exercise. Also, the large variability of physical activity habits in the children in our study gave us a broad activity continuum to examine tidal volume regulation and expiratory flow limitation, which is representative of this population.

In healthy adult populations, EFL during exercise is associated with regulating tidal volume at increased lung volumes (McClaran et al, 1999). Few studies have investigated EFL in children, but a recent study from Nourry et al (2006) shows dissimilar breathing patterns between those who did and those who did not experience EFL. Surprisingly, flow-limited children had significantly lower end-expiratory lung volume, as estimated by ERV/FVC, and higher end-inspiratory lung volume, as estimated by IRV/FVC compared to non-flow-limited children during peak exercise. Nourry et al (2006) attribute this disparity from adult literature to differences in peak ventilation between flow-limited and non-flow-limited children. Higher peak ventilation was demonstrated by non-flow-limited compared to flow-limited children, and conversely, lower peak ventilation was demonstrated by flow-limited children. This is likely due to

mechanical constraints of expiratory flow limitation preventing these children from achieving higher ventilation. Similarly, we used dynamic end-expiratory lung volume (EELV), estimated by ERV relative to FVC (ERV/FVC) to determine tidal volume regulation. Our data contradict these previous results however, and agree with adult evidence, by showing a strong relationship between % EFL during exercise and increased ERV/FVC. We do not have an explanation for the different results in our study and previous reports in children, but we are not aware of any factors to suggest that tidal volume regulation should be different between children and adults.

Consequences of Expiratory Flow Limitation

There are likely several physiological consequences attributed to the high prevalence of EFL during exercise in our subjects. The increase in EELV that occurs with EFL (Lind and Hesser, 1984; Henke et al, 1988) decreases optimal inspiratory muscle length, increasing the work and oxygen cost of breathing, and consequently decreases respiratory muscle endurance. During maximal exercise, most of the children in our study breathed at high lung volumes, indicating the tidal breath was placed near the top of the pressure-volume relationship where lung compliance is decreased, and work of breathing likely increased.

Further, increased minute ventilation has been associated with increased work of breathing in adult men (Milic-Emili et al, 1962; Coast et al, 1993). Guenette et al (2007) introduced the concept of evaluating this relationship in women given their smaller vital capacities relative to height-matched men. It was found that women have smaller airway diameters (Mead, 1980) and total number of airways, implying that the resistance to flow

would be higher during exercise (Otis, 1954). Beyond light intensity activity, women increase their minute ventilation "out of proportion" to men; in fact, beyond 90 L/min, the work of breathing is twice as high in women as men (Guenette et al, 2007). Given similar characteristics of children and women having smaller lung volumes relative to size, it would be expected that the excessive ventilation also seen in children would suggest a higher work of breathing in children compared to adults.

At intensities over 80% of VO_{2max}, the diaphragm is known to fatigue (Babcock et al, 1995). Harms et al (1995, 1997) and Sheel et al (2002) have demonstrated that at fatiguing levels of respiratory muscle work, there are changes in vascular resistance, and a reduction in blood flow to locomotor muscles, limiting exercise tolerance (Harms et al, 2000). These conditions would presumably worsen in populations who showed increased work of breathing (Simon et al, 2001). Because our subjects demonstrated substantial EFL, likely leading to high levels of respiratory work, it would suggest (although not directly measured) that diaphragmatic fatigue occurred in our subjects. Consequently, there may be changes in vascular resistance that limit exercise tolerance in children. This postulate warrants further investigation.

Significant EFL and ventilatory constraints could also affect gas exchange. To our knowledge, there are very few studies that have evaluated exercise-induced arterial hypoxemia (EIAH) or arterial desaturation in healthy, active children (Nourry et al, 2004; Laursen et al, 2002). In the study by Nourry (2004), significant arterial desaturation, measured by pulse oximetry, occurred in seven of 24 prepubescent children. There was a significant association of EIAH with lower FVC and breathing reserve in hypoxemic subjects matched for physical activity. In our study, although significant EFL was observed in both boys and girls, ventilation, pulmonary O_2 diffusing capacity and

pulmonary capillary red blood cell transit time were apparently sufficient to prevent SaO_2 falling significantly. Our subjects did not experience any relative alveolar hypoventilation that would also contribute to EIAH (Harms et al, 1995). The apparent difference between our study and the results of others could potentially be due to the physical activity habits of the subjects. The subjects in the Nourry et al (2004) study were highly active with VO_{2max} values that were higher than ours. EIAH is common in adults who undergo regular training (Dempsey and Wagner, 1999), and training-induced augmentation of aerobic demands may contribute to the onset of EIAH in children. Not withstanding the above, even our subject with the highest VO_{2max} did not demonstrate arterial desaturation at maximal exercise.

Limitations

Several limitations exist that may have influenced our results. First, the results of our study depend largely on the placement of exercising tidal loops within maximal flow volume loops during maximal exercise. There may be considerable variability in tidal volume loop at peak exercise when ventilation is highest. However, we counted a minimum of five breaths prior to having subjects perform the inspiratory capacity maneuver in order to reduce variability. The metabolic cart used in the study also automatically corrects for drift that occurs when there are differences between inspiratory and expiratory volumes. Furthermore, in order to minimize the "learning effect", subjects practiced the maximal, volitional flow-volume loop maneuver until the values were consistent and the subject felt confident. Second, exercise data at VO_{2max} is highly reliant on the maximal volitional effort of the subject. Children may have a different

perception of fatigue and exertion than adults, possibly prematurely ending their exercise test. Those children who were physically active might have had a more accurate maximal exercise test due to the more familiar feeling of exhaustion. However, the agreement in VO_{2max} values between the incremental exercise test and the constant supramaximal load test provides substantial confidence that all subjects were at their VO_{2max}. Although dyspnea values were taken during the exercise test, they were judged unreliable and hence, are not included due to the wide perceptions of fatigue and comprehension of the dyspnea rating scale in children. Finally, pulse oximetry was the method used to determine arterial oxygen saturation, rather than temperature corrected arterial blood samples. Due to ethical constraints in children, pulse oximetry is currently the most acceptable form of measurement for this population. To ensure accurate measurements in our study, pulse oximetry measures were consistently monitored by visual waveform in all test sessions and the sensor was secured to the earlobe to minimize artifact.

Future Directions

The interesting and novel results from our study raise several questions for future research projects. While we found that anthropometric variables were not different between boys and girls, the measurement of thoracic dimensions (Kivastik and Kingisepp, 1997) may provide greater insight in the differences of pulmonary capacity between boys and girls. Further evaluation of EFL in prepubescent children is also needed to understand its high prevalence. Additionally, by eliminating expiratory flow limitation via a low-density HeO_2 inspirate (McClaran et al, 1999), changes in EELV and EILV can be observed to learn more about ventilation and breathing pattern regulation in

response to heavy exercise. Because the percentage of prepubescent children experiencing EFL is high, there could be significant benefits to understanding how EFL affects tidal volume regulation, respiratory muscle work, dyspnea, and changes in peripheral vascular resistance. If respiratory muscle fatigue was properly assessed in children, more research could be done to determine its effect on vascular conductance in the working muscles, and possibly exercise tolerance. Finally, a large-scale longitudinal study that follows prepubescent children through adolescence is needed to determine the mechanisms responsible for the differences in prevalence of EFL and other cardiopulmonary responses between normal, healthy children and adults. It is presently very difficult to compare data across studies due to different protocols, instrument variability, and physical activity status of subjects.

Conclusions

Our results confirm that EFL is common in healthy, prepubescent boys, and we have shown for the first time that the prevalence is also high in girls, regardless of height, weight, or body composition. Differences exist between boys and girls in metabolic demand and pulmonary capacity, the combined effects of which cause the prevalence of EFL to be high and similar. However, ventilatory constraints in prepubescent children do not lower arterial oxygen desaturation, but may increase work of breathing, and consequently, impair exercise tolerance. Although our study indicates similar prevalence rates of EFL in boys and girls, ventilatory constraints are more prevalent in adult women compared to adult men. As children mature into adults, there seem to be dissimilar growth-related changes in the pulmonary system seem between sexes. Further

investigation would be worthwhile to track children through adolescence to determine the prevalence and implications of these documented ventilatory constraints into adulthood.

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