VENTILATORY MECHANICS IN ENDURANCE ATHLETES

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ABSTRACT

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The lungs were once thought to be over-built for exercise. However, upon further research, endurance athletes have been found to reach their maximum ventilation, demonstrating an insufficiency of the lungs to accommodate the demands of highly demanding endurance sport. This knowledge has inspired researchers to look further into the exercise ventilatory responses and, in doing so, researchers discovered that the adaptations of the pulmonary system to endurance training are still not well understood. Potential reasons for this lack of knowledge may be methodological measurement limitations, as ventilatory mechanics have been measured classically either invasively or by breathing maneuvers. These measurements are difficult to perform during high intensity exercise and in large groups of athletes. However, recent innovations in motion analysis technology have allowed for ventilatory mechanics to be measured during high intensity exercise, potentially allowing for further insight into how high intensity endurance training impacts ventilatory mechanics.

The purpose of this study is to describe normal ventilatory mechanics during exercise in endurance trained and healthy untrained individuals, explore potential gender differences during exercise and investigate the impact of flow limitation during exercise on ventilatory mechanics, using a motion analysis system that allows researchers to obtain information on chest wall volume changes and chest wall compartmental interactions during high intensity exercise. This motion analysis system is called Optoelectronic Plethysmography (OEP).

This dissertation is comprised of an introduction to the work and the 3 projects that comprise the dissertation along with an appendix, which includes a complete literature review. The three projects are as follows (1) an introduction to motion analysis as a tool in measuring ventilatory mechanics, (2) research determining the differences in the ventilatory mechanics in endurance athletes and healthy controls from rest to maximal exercise and (3) the differences in ventilatory mechanics between endurance trained women who demonstrate expiratory flow limitation during high intensity exercise versus endurance trained women who do not.

Project 1: Optoelectronic Plethysmography (OEP) is a motion analysis tool that can be used to define exercise ventilatory mechanics by analyzing chest wall movements and calculating volume changes. By analyzing breathing mechanics by motion analysis rather than traditional breathing maneuvers, individual components of the chest wall can be analyzed and changes in volume throughout the chest wall can be assessed without altering the individual's natural breathing pattern. This review presents the history and development of OEP technology, along with a summary of the methods used and a discussion of findings to date, giving insight into exercise ventilatory mechanics never investigated before.

Project 2: Differences between the ventilatory mechanics of endurance athletes and non athletes using motion analysis have not yet been described. To determine how increased ventilatory demand impacts ventilatory kinematics, we compared the total chest wall volume variations (V_{CW}) of 18 male and female endurance-trained athletes (ET) to 14 untrained individuals (UT) during exercise. We hypothesized that training and gender would have an effect on V_{CW} and kinematics at maximal exercise. Gender and training significantly influenced chest wall kinematics. Female ET did not change chest wall end-expiratory volume (V_{CW},ee) or pulmonary ribcage end-expiratory volume (V_{RCp},ee) with exercise, while female UT significantly decreased

V_{CW},ee and V_{RCp},ee with exercise ($p<0.05$). Female ET significantly increased pulmonary ribcage end-inspiratory volume (V_{RCp},ei) with exercise ($p<0.05$), while female UT did not change V_{RCp},ei with exercise. Male ET significantly increased V_{RCp},ei with exercise ($p<0.05$); male UT did not. Men and women had significantly different V_{CW} ($p <0.05$). Women demonstrated the greatest variation of V_{CW} in the pulmonary ribcage compartment (V_{RCp}). Men had similar volumes in the V_{RCp} and the abdomen (V_{Ab}). In conclusion, gender and training had a significant association with ventilatory kinematics.

Project 3: Research has found potential limitations of the airways to accommodate the large tidal volumes generated during high intensity exercise. This airway limitation has been defined as expiratory flow limitation (EFL) observed during high intensity exercise in a large percentage of healthy women. Because of endurance athletes' ability to exercise at high intensities for prolonged periods of time and produce greater than average tidal volumes, female endurance athletes may be particularly susceptible to EFL and the impact EFL may have on performance. The purpose of this last chapter was to investigate the ventilatory mechanics and exercise capacity parameters of female endurance athletes with and without EFL. Female competitive cyclists participated in two days of testing; day one consisted of a maximal aerobic capacity test ($o_2$max test) with spirometry and day two involved chest wall motion analysis testing during two steady state exercise tests. Baseline flow volume loops were performed prior to exercise and repeated post exercise. During exercise participants performed flow volume loops at minutes 4, 6, 8 and last 30 seconds of exercise. EFL was considered present when the exercise flow volume loop surpassed the baseline flow volume loop. To quantify the degree of flow limitation when comparing the peak exercise flow volume loop to the baseline flow volume loop, we calculated the percent flow volume loop reserve (%FVL reserve). Two levels of submaximal constant-load

exercise bouts (at 60% and 85% maximal watts) were employed to investigate if EFL impacted ventilatory mechanics differently at different intensities. Optoelectronic plethysmography (OEP) was employed to measure V_T from the pulmonary ribcage (V_{RCp}), abdominal ribcage (V_{RCa}) and the abdomen (V_{Ab}), as well as to measure end-expiratory volume chest wall volume (EEV) to calculate potential dynamic hyperinflation. Comparison of participants with and without EFL was made using an ANOVA or Kruskal-Wallis test ($p \leq 0.05$). Predictors of %FVL reserve were explored with a multiple linear regression. Two participants were not included in the data analysis due to the presence of asthma (one at rest, one exercise induced) as determined by spirometry during day one testing. Out of the other 28 participants, 6 participants had definite EFL (DEFL) demonstrated by overlapping of the peak exercise flow volume loop with the pre and post exercise flow volume loop, 5 had borderline EFL (BEFL) demonstrated by an overlapping of only the pre exercise flow volume loop and 17 had no EFL (NEFL) demonstrated by no overlapping of the pre or post flow volume loops. All participants had within normal limits of the percent predicted normal reference values in resting forced expiratory volume in 1 second (FEV_1), forced mid expiratory flow rates (FEF_{25-75}L/sec), forced vital capacity (FVC) and FEV_1/FVC ratio. DEFL and BEFL participants' had a significantly lower FEV_1/FVC ratio compared to NEFL ($p=0.003$), DEFL had significantly lower FEF_{25-75}% predicted normal reference values before and after exercise compared to NEFL ($p=0.004$). There were no differences in the exercise capacity values between groups. During the day two steady state tests, there was a significant interaction effect between groups and exercise intensity in the $\%V_{RCa}$ ($p=0.045$) and $\% V_{Ab}$ ($p=0.049$). End-tidal carbon dioxide pressure, FEF_{25-75}%, history of self reported excessive mucus with exercise and $\% V_{RCp}$ during the 85% constant load test explained 71.6% of the variability in %FVL reserve in our regression model ($p=0.002$). Independent

predictors of %FVL reserve were: end-tidal carbon dioxide pressure (p=0.033), FEF_{25-75}% (p=0.010) and history of excessive mucus with exercise (0.014). In conclusion, female endurance athletes demonstrating EFL had normal but significantly different FeV_1/FVC ratio and significantly different abdominal ribcage and abdomen percent contribution with increased exercise intensity, but similar exercise capacities compared to the female endurance athletes with no EFL. Also, independent predictors of %FVL reserve were found to be FEF_{25-75}%, history of mucus production with exercise and end-tidal carbon dioxide level at peak exercise.

This dissertation has provided further insight into the ventilatory mechanics of endurance athletes and how potential airway limitation can impact high intensity exercise. Further research can seek to better understand if the differences in ventilatory mechanics between endurance athletes with EFL and no EFL allow for preservation of exercise capacity in the presence of airway limitation.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

ACKNOWLEDGEMENTS

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CHAPTER I

INTRODUCTION

Purpose of the study

The purpose of this dissertation is to determine the normal ventilatory mechanics of people during exercise, then expand on that knowledge to determine how ventilatory mechanics are altered in the presence of natural expiratory flow limitation observed during exercise (EFL). Current literature under represents the impact of training and gender on volume distribution within the thoraco-abdominal compartment and how a person's ability to generate and alter tidal volume impacts exercise.

Rationale

This research can be used to further understand gender differences in ventilatory mechanics, how endurance exercise impacts ventilatory mechanics and how ventilation may impact the continuation of exercise. Specifically this project will investigate how flow limitations in women impact ventilatory mechanics and exercise tolerance. The design of this study can be replicated in women with chronic obstructive pulmonary disease (COPD) to study how various medications may benefit or hinder exercise tolerance.

Research Questions

1. How does Optoelectronic Plethysmography (OEP) measure ventilatory mechanics and has it been proven a valid and reliable tool for the purposes of analyzing ventilatory mechanics?

2. Are there differences between resting ventilatory mechanics and exercise in healthy individuals?
3. Are there differences between the ventilatory mechanics of endurance athletes and untrained healthy individuals?
4. Are there differences between the ventilatory mechanics of men and women during exercise?
5. Do all female endurance athletes demonstrate expiratory flow limitation?
6. Do the flow limitations in female endurance athletes result in altered ventilatory mechanics?
7. Do alterations in ventilatory mechanics form EFL lead to ventilatory limitation to exercise?
8. Are female endurance athletes with EFL more symptomatic (symptoms similar to exercise induced asthma) than those with no expiratory flow limitation (NEFL)?

Dissertation Organization

The above questions were answered in three related ways studies that follow in chapter II (question 1), chapter III (question 2, 3 and 4) and chapter IV (questions 5, 6, 7, and 8). This dissertation uses the article format of the journal in which the study was published, or in the case of the final project, the journal to which the study will be submitted for publication. A comprehensive literature review on endurance athletes' ventilatory mechanics is found in Appendix A.

CHAPTER II

An Assessment of Pulmonary Function Testing and Ventilatory Kinematics by Optoelectronic Plethysmography

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ABSTRACT

New advances in computer processing and imaging have allowed the development of innovative techniques to assess lung function. Among the most interesting of these new methodologies is Optoelectronic Plethysmography (OEP). OEP utilized infrared imaging with markers placed on the chest, back and abdomen of subjects in order to evaluate ventilatory kinematics. Currently this system is used mostly in research settings but may have broad applicability in patient populations such as children, neuromuscular disease and patients who cannot perform classical spirometry. This review presents the history and development of the technology, along with a summary of the method and a discussion of some of the research findings and results to date.

INTRODUCTION

The most common form of lung function testing is spirometry. Spirometry measures the volume, speed and frequency of the ventilatory cycle using a pneumotachograph, mouthpiece and nose clip (1). Although this technique is well known and reliable, recent findings demonstrated that this system alters the natural breath frequency (f_B), tidal volume (Vt), dead space ventilation and breath awareness which may cause hyperventilation and altered breathing patterns that aren't truly natural (1, 2). For this reason, alternative methods to measure lung function have evolved. One of the newer methodologies is Optoelectronic Plethysmography (OEP), which uses motion analysis technology. The term optoelectronic refers to the sensor system being used and plethysmography refers to the acquisition of volume. OEP uses a series of infrared cameras, reflective markers and motion capture software originally developed for biomechanical analysis to measure lung volumes and variations in ventilatory kinematics. The term "kinematics" refers to the motion or displacement and is often used in biomechanics. Over the past ten years, OEP has been utilized in research settings and in several patient populations (3-7).

Historical Development

In 1966, an original article written by Konno and Mead describes the technique of acquiring lung volumes based on analyzing the movement of the ribcage and abdomen using direct writing recorders that plot X-Y axis coordinates of the thoracic dimensions (x is the transverse plane and y is the sagittal) to estimate changes in volume (8). Other researchers applied Konno and Mead's technique to motion analysis and devised a system that could estimate lung volumes. The first motion analysis system used to test lung function was a linear

magnetometer. The linear magnetometer uses tuned coils placed on the anterior and posterior thorax to measure the cross sectional area of the rib cage and abdomen to estimate Vt (9). A major limitation of linear magnetometry is that it does not differentiate between the pulmonary ribcage, the abdominal ribcage and the abdominals. Measuring the abdominal ribcage can represent the movement of the diaphragm (10) which can vary with disease and gender.

To resolve this problem, another system was developed called "The ELITE" (ELITE system, BTS, Milano, Italy) (11). The ELITE's technology is based on a digitized video system and automatic motion analyzer to identify objects of predetermined shape (such as the person's chest) and monitor their trajectories in 3-D and in real time. Researchers applied this technology to calculate the movements of the pulmonary ribcage**,** abdominal ribcage and abdomen using an algorithm originally developed to measure movements of the joints and limbs (11). The ELITE system uses 32 reflective markers; cameras and video images to create real time, recordings of the chest, posterior thorax and abdomen. The coordinates of each marker are recorded by infrared cameras and processed by a computer algorithm for 3-dimensional reconstruction of the chest wall. In this manner, the system can estimate the volumes by changes in the dimensions of the chest wall. Although this system was able to obtain lung volumes, the error was unacceptably high (± 21.3%) compared to traditional spirometry (9).

A refinement to the original ELITE system, Cala et al developed a method of using 86 markers and circumferential geometry using Gauss's theorem in the computer algorithm, rather than cubic geometry, to improve accuracy by more accurate measurement of the shape of the chest wall (9, 11, 12). In fact, the 86 markers set up successfully decreased the error to < 3.5%, compared with pulmonary function measurements. Cala's refinement of the ELITE technology was patented under a new name, Optoelectronic Plethysmography System, or OEP (BTS

bioengineering s.p.a, Milano Italy) (10). The original capture system for OEP used 4 cameras (2 with an anterior view and 2 with a posterior view) and 86 markers (43 anterior, 10 lateral, 34 posterior) (6, 10). In 2002 Alverti et al describe using 89 markers (42 anterior, 10 lateral and 37 posterior) and 6 cameras method of data acquisition to improve accuracy (12).

METHODOLOGY

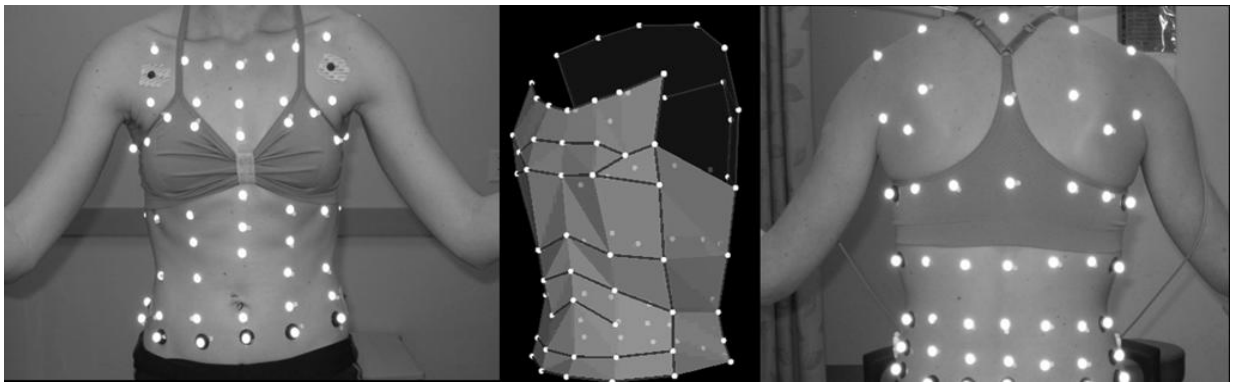
Camera System

The most recent OEP system uses 8 cameras for improved ability to track the markers. The 8 cameras are set up in a circular pattern at approximately head height and at a distance of 4 meters from the individual being measured, with 4 cameras arranged in front and 4 placed behind the subject.

Markers

The system uses 89 markers that are 6 mm in diameter, with 79 semi-hemispherical and 10 spherical. The markers are placed on the skin by bi-adhesive hypoallergenic tape in a grid system (10, 12, 13). The grid consists of seven horizontal rows between the level of the clavicles and the anterior superior iliac crest with additional bilateral columns in the midaxillary line to create the anterior view, and on the posterior aspect, there are seven posterior horizontal rows between C7 and the posterior axillary lines (14). (See Figure 2.1)

Figure 2.1 Woman subject with the 89 marker set up and 3D chest reconstruction.



Front and back view of subject with 89 marker set up. Center of figure depicts the 3 dimensional reconstruction of this subject.

Calibration

There is a 2 part calibration of the equipment which involves calculating the 3-D position of a calibration tool. The tool has a markers in the x, y and z axes (figure2). Step one is having the system recognize all three axes with each camera. If one axis cannot be recognized, the cameras must be repositioned and step one repeated. Step 2 involves taking the y-axis of the tool (the wand) and moving it within the space that the subject will be placed. The cameras must be detecting the wand as it moves throughout the space for calibration to be complete. If the wand could not be detected than the cameras must be focused or the technician varies his/her technique such as moving slower with larger movements (11). Once the system is calibrated (which takes less than a minute and a half), it is ready to measure breath-by breath lung volume changes.

Volume Measurements

Change in chest wall volumes measurements are divided into 3 compartments: the pulmonary rib cage (ΔV_{RCp}), abdominal ribcage (ΔV_{RCa}) and the abdomen (ΔV_{AB}). The pulmonary ribcage region begins at the clavicles and jugular notch and terminates at the xiphoid;

the abdominal ribcage region is separated from the pulmonary ribcage at the xiphisternum and terminated at the lower costal margin; the abdomen region begins at the lower costal margin and terminates between the bilateral anterior superior iliac crests. The compartments can be further divided into the right and left side to distinguish any variations between the right and left lung volumes. Lung volumes are calculated based on the displacement of the triangulated surface area, as described in detail in the original publications describing OEP (10, 12, 15).

Unlike spiromtery, OEP can measure lung volumes during exercise, various breathing maneuvers and rest. Like spirometry, OEP can also calculate flow changes so all of the common breathing maneuver measurements can be made (14).

VALIDITY/RELIABILITY

Volumes acquired by OEP demonstrated a strong correlation with volumes obtained by spirometry during quiet breathing and the vital capacity maneuver (6). OEP has also been validated for intensive care patients, infants and chronic obstructive pulmonary disease patients (3, 5, 16, 17). OEP has also been validated in the prone and supine positions and there were no significant effects of position on volumes or kinematics (3).

The retest reliability of OEP was tested by Viera et al. in 9 males and females at rest and during exercise. OEP was found to have a $\leq$ 10% trial to trial variation under both resting and exercise conditions. Thus conclusions that OEP presented good reliability for the assessment of young healthy subjects at rest and during exercise (18).

APPLICATIONS

OEP has been used predominantly for research, but the available studies show promise for the potential application in pulmonary volume assessment in varied clinical settings. Recent studies in clinical populations have used OEP to evaluate pulmonary mechanical function and identify changes from procedures, medications or other treatments.

OEP has been able to consistently detect changes in dynamic lung hyperinflation with exercise. A study by Vogiatzis et al. evaluated dynamic lung hyperinflation during incremental cycling testing using OEP (19). During exercise, patients exhibited one of two different patterns of dynamic hyperinflation: "early hyperinflators" who demonstrated progressive increases in end-expiratory chest wall volumes at the onset of exercise, and "late hyperinflators" who had increases in end-expiratory chest wall volumes in the last third of exercise. Although the subjects with early hyperinflation exhibited significantly greater end expiratory lung volume and retained these volumes for several minutes after exercise, both groups achieved the same peak work rate (19).

Extending the work of Vogiatzis and colleagues, Alverti et al found that COPD patients who demonstrated early increases in end-expiratory lung volumes during the onset of exercise (i.e., early hyperinflation) also demonstrated a paradoxical diaphragmatic breathing pattern (5). This pattern was maintained throughout the incremental cycling test. In contrast, this paradoxical breathing pattern was not observed in patients who decreased end-expiratory volumes and presented a more normal lung volume dynamic. The effects of bronchodilators on the kinematics of the hyperinflated lungs were studied in a follow up study by the same research group, and the abnormal breathing kinematics seen in the hyperinflated lungs of a COPD patient was decreased after taking bronchodilator (20).

The ability of OEP to distinguish the ventilatory kinematics between the right and left lung was used in a study investigating the effects of pulmonary rehabilitation after right or left superior lobectomies (21). Patients demonstrated a 32% greater utilization of non-operated side lung volume following pulmonary rehabilitation, suggesting that the non-affected lung compensates for the operative lung (21). OEP was also used in another study to investigate the effects of pulmonary rehabilitation in patients' with COPD (22). OEP was able to distinguish patterns of progressive dynamic hyperinflation during progressive exercise testing before and after rehabilitation. By using OEP, researchers were able to detect a reduction in abdominal volumes after a 12 week pulmonary rehab program (22).

STRENGTHS and LIMITATIONS of OEP

OEP has both strengths and limitations. OEP gives an ability for pulmonary volume measurements in individuals who would otherwise not be able to have testing, such as in patients with the inability to form a tight seal with the mouthpiece or patients who are unconscious. But beyond this, OEP gives the ability to measure breathing kinematics. OEP can be used to analyze the effects of surgery on breathing kinematics. For instance, OEP can be used to assess the effects of obesity or abnormal body habitus, chest deformities, single and double lung transplants, diaphragmatic paralysis, bulbar ALS, lung volume reduction surgery on dynamic hyperinflation, different levels of paralysis, and exercise on breathing kinematics.

As evidence of increased application of OEP, at the 2010 European Respiratory Society conference, ten different posters or platform seminars presented results of OEP. The topics ranged from muscle training in fit healthy subjects to the breathing kinematics of patients with tertraplegia, chronic obstructive pulmonary disease, and cardiomyopathies.

However some of the limitations of the technique include several issues related to marker placement. Marker placement is complicated and can be tedious. The precise placement of the markers involves significant practice to correctly identify the anatomical locations, combined with thorough understanding of the operation of system. Errors in marker placement, even as little as a millimeter, can cause a marker to be unrecognizable by the system. If such errors occur, the operator must be very familiar with the marker matrix and the slight adjustments that must be made to produce an accurate data acquisition. Errors in the marker recognition can also occur during a trial. If a marker is blocked from the camera field, the system will render the matrix indecipherable and the markers will have to be manually given values. This task can be extremely tedious if the file is large or many markers were blocked. Although the amount of error introduced to the data is minimal when this occurs because there are so many data points and acquisition frames (3, 13).

The purchase and set up costs of the OEP are substantial, and at the present time OEP has not been approved by the Centers for Medicaid and Medicare Services (CMS) as a recognized billable procedure, but it can be billed as a full pulmonary function test.

There is also a practicality issue of the system. OEP requires the subject or patient to be bare chested for the marker placement and data acquisition. Some woman may not be comfortable with this aspect of the test. In order to respect a woman's privacy or comfort level, OEP may need a female technician to be available when necessary. This may require additional staff being available for testing.

CONCLUSION

Advances in computer technology and motion analysis have enabled OEP to become a new tool for investigating many aspects of ventilatory kinematics and treatment of disease. Since OEP is noninvasive it presents potential advantages in the evaluation of critical care patients, infants, patients with neuromuscular disease such as muscular dystrophy and motor neuron disease, as well as in being able to measure lung volumes during sleep and exercise. OEP is an accurate and innovative resource for evaluating the physiological components of respiration under many conditions. As a tool, OEP can be used to assess lung volumes in a unique manner that may be beneficial for various population and environments that lung volumes could not be measured in using previously known techniques.

CHAPTER III

Exercise ventilatory kinematics in endurance trained and untrained men and women

Publication reference: Layton AM, Garber CE, Thomashow BM, Gerardo RE, Emmert-Aronson BO, Armstrong HF, Basner RC, Jellen P, Bartels MN. Exercise ventilatory kinematics in endurance trained and untrained men and women. *Respir Physiol Neurobiol.* 2011 Jun 17.

ABSTRACT

To determine how increased ventilatory demand impacts ventilatory kinematics, we compared the total chest wall volume variations (V_{CW}) of male and female endurance-trained athletes (ET) to untrained individuals (UT) during exercise. We hypothesized that training and gender would have an effect on V_{CW} and kinematics at maximal exercise.

Gender and training significantly influenced chest wall kinematics. Female ET did not change chest wall end-expiratory volume (V_{CW},ee) or pulmonary ribcage (V_{RCp},ee) with exercise, while female UT significantly decreased V_{CW},ee and V_{RCp},ee with exercise ($p<0.05$). Female ET significantly increased pulmonary ribcage end-inspiratory volume (V_{RCp},ei) with exercise ($p<0.05$), while female UT did not change V_{RCp},ei with exercise. Male ET significantly increased V_{RCp},ei with exercise ($p<0.05$); male UT did not. Men and women had significantly different variation of V_{CW} ($p <0.05$). Women demonstrated the greatest variation of V_{CW} in the pulmonary ribcage compartment (V_{RCp}). Men had even volumes variation of the V_{RCp} and the abdomen (V_{Ab}).

In conclusion, gender and training had a significant impact on ventilatory kinematics.

INTRODUCTION

During high intensity exercise, well-trained endurance athletes can utilize near maximum levels of ventilation (23-30). The impact of extreme ventilatory demands on tidal volume (Vt) and breathing mechanics has been studied, but the findings have been inconsistent. Some studies have found that athletes exhibit larger V_t during exercise compared with inactive individuals (26, 31, 32), while others have demonstrated higher respiratory rates and similar V_t (33). Some studies also have reported mechanical constraints in female athletes as the athletes approach their maximal expiratory air flow (28, 34). More conclusive evidence is needed to determine the interactions among gender, training status and the ventilatory response to maximal exercise.

Recent innovations in technology have enabled the measurement of exercise breathing patterns and chest wall volumes. We defined the volume-motion relationship (8) using the term ventilatory kinematics, this usage of the term is similar to past work regarding chest wall motion analysis (18, 35). We used Optoelectronic Plethysmography (OEP) to measure the chest wall kinematics of our subjects during exercise. OEP is an innovative biomechanical motion analysis system using 3-dimensional camera reconstruction of digitized images to calculate the movement of the entire chest wall and its rib cage and abdominal compartments. OEP has enabled us to determine exercise chest wall volumes (V_{CW}) and its three main compartments: 1) pulmonary ribcage variation (V_{RCp}), 2) abdominal ribcage variation (V_{RCa}), 3) abdomen variation (V_{Ab}) (36).

Previous work using OEP has demonstrated variations in the ventilatory kinematics between women and men at rest (37). This variability between genders becomes especially exaggerated during exercise. Women may have upper airways mechanical constraints that could impact chest wall kinematics and change volumes (6, 28, 29, 34, 38-41).

Therefore, this study primarily aimed to investigate exercise chest wall kinematics in endurance athletes compared to untrained healthy controls. We hypothesized that endurance athletes would demonstrate larger dynamic chest wall volume than untrained controls, which would primarily arise from abdomen and abdominal ribcage variation. The secondary aim of this study was to compare the chest wall volume and kinematics between women and men to test interactions between gender and training. We hypothesized that gender would have an effect on changes in chest wall volume and kinematics.

METHODS

Recruitment

Endurance trained athletes (ET) and untrained controls (UT) were recruited from the New York City metropolitan area. ET subjects were recruited through local cycling and triathlon teams and UT subjects were recruited among students, faculty and staff at Columbia University.

IRB committee approval

This study was approved by the Columbia University Medical Center's institutional review board for human subject testing. All subjects signed informed consent.

Study design

The study used a two by two by one non-experimental design. The objective of this study was to investigate the differences in ventilatory kinematics between endurance athletes and untrained controls during a maximal exercise test.

Study Overview

Testing involved one visit to the laboratory. Upon arrival, subjects first performed a pulmonary function test, after which we prepared them for OEP testing by placing OEP reflective markers on their trunk and conducting a camera calibration. Next, we positioned each subject on the exercise bicycle and conducted final pre-testing preparation as described in further detail below.

Exercise Testing

Prior to testing, maximum voluntary ventilation (MVV) was measured using the Vmax Encore Metabolic Cart (Care Fusion, Palm Springs, CA 92262). If a subject exhibited an MVV below 80% predicted, the technician performed spirometry to screen for marked ventilatory abnormality.

Following the MVV test, subjects completed maximal graded exercise tests on an electromagnetically braked cycle ergometer (Viasprint 2900, Care Fusion, Palm Springs, CA 92262). Testing protocol consisted of 5 minutes of resting baseline measurements, 3-minutes of warm-up, and a ramping resistance cycling stage, followed by active recovery of 3-5 minutes (42). We determined the ramping protocol for UT by calculating the normal predicted peak workload (watts min^{-1}) estimated using each subject's age, weight and gender, and dividing the result by ten to attempt to attain maximal exertion within 6-12 minutes (43). For ET, who presumably had higher fitness levels, we used a ramping protocol of 25 watts min^{-1} for women and 40 watts min^{-1} for men, also to achieve a maximal exertion within 6-12 minutes (30, 44). Breath-by-breath pulmonary gas exchange samples were measured using the Vmax Encore Metabolic Cart and were averaged every 20 seconds. The technician measured heart rate (HR) using a 4 lead electrocardiogram (Cardio V4 MDL37 ECG, Cardiosoft, Houston, TX 77056).

Variables collected included oxygen uptake (VO_2), carbon dioxide output (VCO_2), respiratory exchange ratio (RER), minute ventilation (Ve), and ventilatory equivalent for carbon dioxide (Ve/VCO_2) and oxygen (Ve/VO_2). The technician terminated exercise at RER >1.1 and HR> 90% predicted maximum (220-age) (45), combined with voluntary fatigue, which was defined as the inability to maintain a cadence of greater than 40 rpm. Ratings of perceived exertion were not assessed during testing because their acquisition would have interfered with OEP camera views. VO_2max and ventilatory threshold (VT) (using the V-slope method (46)) were identified by the laboratory medical director and laboratory exercise physiologist. VT is the ventilatory threshold, a point during submaximal exercise that is approximately equal to lactate threshold, a level of exertion that is sustainable during exercise training in athletes and non-athletes alike. We choose this point because it occurs precisely before ventilation substantially increases.

Ventilatory Kinematics

OEP calculates absolute and relative volume changes of the chest wall. The method by which OEP calculates chest wall kinematics has been described in prior work (4, 10, 36). V_{CW} is divided into its different thoraco-abdominal compartments, pulmonary ribcage (volume in the upper portion of the chest where flow is generated), abdominal ribcage (the mid portion and the abdomen where the diaphragm is attached), and the abdomen. The ventilatory kinematics describe the change the average contribution of the compartments to V_{CW} variations (47).

OEP set-up consists of placing 89 reflective markers on the subject's chest, abdomen and back in order to map the subject's trunk. The markers followed a grid using anatomical references as a guide. This technique has been shown to be valid in both healthy and clinical populations at rest and during maximal exercise (20, 48-51).

Absolute Volumes

We collected absolute end-inspiratory chest wall volumes (V_{CW},ei) and end-expiratory chest wall volumes (V_{CW},ee). The V_{CW},ei and the V_{CW},ee were expressed as both total volume and compartmental volume variation, and were analyzed at rest and during the last minute of exercise.

Statistical Analysis

Statistical analyses were performed using SPSS version 18.0. Predicted MVV was calculated using references from Kory et al for men and Morris et al for women (52, 53). Breathing reserve (BR) was determined as %BR= (1-(Ve /MVV)*100) (54).

Descriptive statistics are reported as means and standard deviations. Repeated measure ANOVAs with two between subject factors (sex: male and female; and training: trained, untrained) and one within factor (either chest wall tidal volume or kinematics) with 3 levels (pulmonary ribcage, abdominal ribcage, abdominals) were used to test our hypotheses. A test of within subjects contrast investigated the differences between resting, VT and peak exercise kinematics. Statistical significance was set *a prior*i at $p \leq 0.05$ for all analyses. Mauchly's test of sphericity was performed to correct for variability in error of repeated measures and the Huynh-Feldt correction was used to correct for variability in experimental error over time. A Bonferroni correction was applied to these analyses, and they were tested at p = .00833.

A post hoc analysis of each subject's resting and exercise absolute chest wall volumes (end-inspiratory volume and end-expiratory volume) was performed whenever there were significant main effects. Non-parametric related sample t-tests were used to compare the resting

and exercise V_{CW},ei and V_{CW},ee within the trained males, untrained males, trained females and untrained females. Significance was set at $p<0.05$).

RESULTS

Subjects

Subject demographics are shown in Table 3.1.

TABLE 3.1 Subject Characteristics

Group ET (n=18)	**Age (yr)**	**BMI**
Men (n=11)	30 ± 5.5	23.5 ± 1.2
Women (n=7)	29 ± 5.0	23.1 ± 2.5
Total	29 ± 5.7	23.3 ± 1.7
Group UT (n=14)		
Men (n=9)	25 ± 6.1	23.7 ± 2.1
Women (n=5)	27 ± 7.0	23.8 ± 2.8
Total	25 ± 6.1	23.5 ± 2.3
p<.05§	NS	NS

Table values are Means and standard deviations. No significant differences between groups. ET, endurance trained group; UT, untrained control group. BMI = Body Mass Index

All subjects by study design were between the ages of 18-40 years of age, free from cardiac, pulmonary, musculoskeletal and metabolic diseases, or other limitations to exercise. UT subjects reported performing less than two days (<20 min per day) of aerobic exercise per week and had never competed in an endurance sport. The ET subjects exercised >10 hrs or 100+ miles of cycling per week and were competitive athletes.

Of the forty subjects recruited (20 endurance athletes, 20 untrained controls), thirty-two participants completed the study: 18 ET (11 men, 7 women), and 14 UT (9 men, 5 women). A

prescreening was performed following the guidelines of the American College of Sports Medicine (43) Subjects excluded or who withdrew from testing were: one UT subject with high blood pressure, one ET with asthma, one ET who could not tolerate the mouth piece; five UT completed screening but declined testing. These eight subjects (all male) recruited, but not included in our data, were not significantly different from the study population (data not shown).

Ventilatory and Exercise Capacity

Baseline MVV of the ET and UT showed similar results (Table 3.2).

TABLE 3.2: Rest, submaximal and peak exercise pulmonary function and metabolic parameters.

		Training Status		Sex	
STAGE	**PARAMETER**	**ET**	**UT**	**Men(ET+UT)**	**Women(ET+UT)**
REST	**Ve (L·min)**	10.8 ± 2.4	10.9 ± 3.1	11.6 ± 2.4	8.8 ± 1.6†
	MVV ($L \cdot min^{-1}$)	169 ± 38	157 ± 40	190 ± 27	128 ± 19†
Submaximal (VT)	**VO_2 ($ml \cdot kg \cdot min^{-1}$)**	41.5 ± 6.0	20.7 ± 5.3	37.0 ±14.4	30.5 ± 11.9
	Ve($L \cdot min^{-1}$)	77 ± 13	38.6 ± 9.9	74.3 ± 30.3	55.0 ± 23.0
	V_t (L)	2.57 ± .7	1.43 ± .4	2.4 ± .9	1.7 ± .6
	Ve/VCO_2	24.2 ± 1.9	25.6 ± 3.0	24.5 ± 3.0	25.9 ± 2.1
	Ve/VO_2	24.9 ± 2.8	26.8 ± 3.4	25.2 ± 3.8	27.2 ± 2.8
	Work(Watts $\cdot min^{-1}$)	242 ± 44	113 ± 37	228 ± 94	159 ± 71
	HR ($b \cdot min^{-1}$)	157 ± 12	134 ± 24	152 ± 22	150 ± 21
PEAK	**VO_2($ml \cdot kg \cdot min^{-1}$)**	56.4 ±8.5	36.2 ±7.2*	51.5 ± 12.5	40.9 ± 11.4†
	Ve ($L \cdot min^{-1}$)	129.9 27.6	87.0 ± 21.6*	138.8 ±34.9	95.6 ± 26.4†
	V_t(L)	2.8± .61	2.2± .5*	2.8± .6	2.1± .4†
	Ve/VCO_2	30.7 ± 2.8	29.5 ± 4.1	29.9± 3.6	28.9± 4.1
	Ve/VO_2	35.3 ± 3.0	37.2 ± 7.2	37.1 ± 5.4	36.1 ± 7.2
	Work(Watts $\cdot min^{-1}$)	377 ± 98	201 ± 50*	344 ± 117	244 ± 82†
	HR ($b \cdot min^{-1}$)	185 ± 9	181 ± 12	184 ± 12	181 ± 9

	RER	1.14 ± .07	1.26 ± .07*	1.20 ± .08	1.20± .1

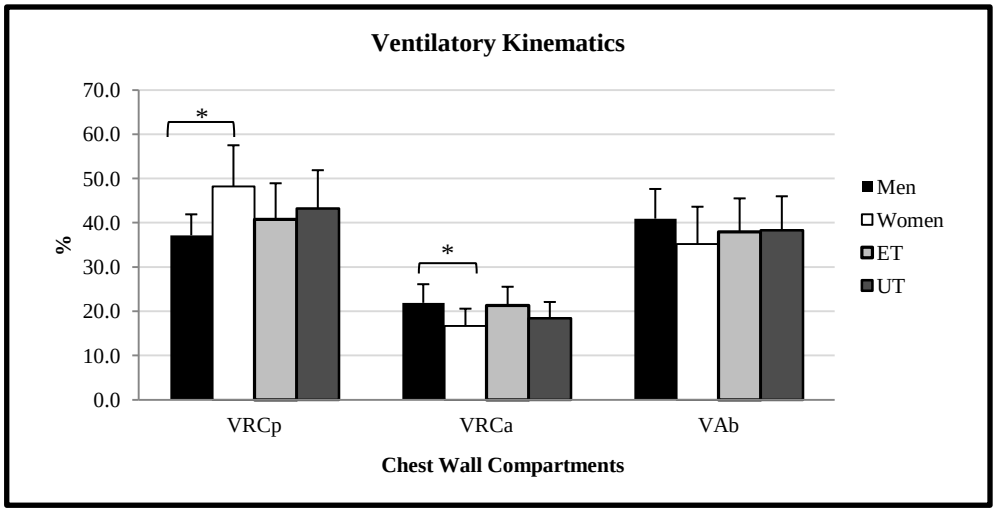
Table values are means standard deviations Table abbreviations: ET: endurance trained athlete; UT, untrained control; Ve, minute ventilation; V_t, tidal volumes; MVV, Maximum voluntary ventilation; VO_2, oxygen uptake; Ve/VCO_2, ventilatory equivalent for carbon dioxide; Ve/VO2, the ventilatory equivalent for oxygen; Work, watts subject achieved at maximal exercise; HR, heart rate; RER, respiratory exchange ratio.VT, ventilatory threshold; PEAK, peak exercise.* $p \leq 0.05$; comparing ET with UT †$p \leq 0.05$; comparing women with men.

All MVVs were above 80% of predicted normative values, indicative of normal lung function (52, 53). For metabolic testing results see Table 3.2. Both groups achieved a peak heart rate (HR) (ET 102 ± 4%, UT 99 ± 25%) near that predicted by using the equation 220-age (45), and a concomitant peak respiratory exchange ratio of $\geq$1.15 (43, 54). ET had significantly less breathing reserve at peak exercise compared to UT (ET 15% ± 14%, UT 39%± 12%, $p<0.001$).

Kinematics

Significant differences were observed between the kinematics of men and women ($p<0.05$). Women had less contribution of the V_{Ab} and greater contribution of the V_{RCp} ($p<0.05$) (see table 3.3). Men demonstrated similar contribution of the V_{RCp} and the V_{Ab}. Difference in the variations from the V_{CW} compartments was significantly greater in V_{RCp} and V_{RCa} in women than in men. The contribution of V_{Ab} was similar between men and women (figure 3.1).

Figure 3.1. Contribution of V_{CW} compartmental variation.



Significance is set at *p<0.05.* Significant differences between men and women. The differences between men and women were constant during rest, ventilatory threshold and peak exercise. Kinematics between ET and UT remained constant during rest, ventilatory threshold and peak exercise. Abbreviations used in table: V_{RCp}, contribution from the pulmonary ribcage volume change; V_{RCa}, contribution from the abdominal ribcage volume change; V_{Ab}, contribution from the abdomen volume change. VT, ventilatory threshold; ET, endurance trained; UT, untrained controls. Men are combined ET and UT. Women are combined ET and UT.

The pattern described above did not alter between rest, VT and peak exercise (table 3.3).

TABLE 3.3. Rest, submaximal (VT) and peak exercise ventilatory kinematics.

STAGE	Men (ET+UT)	Women (ET+UT)
Rest		
V_{RCp}	40% ± 10.4	51% ±10.1*
V_{RCa}	20% ±3.9	17% ± 5.2 *
V_{Ab}	40% ± 12.4	32% ± 9.1
Submaximal (VT)		
V_{RCp}	37% ± 5.4	49% ± 9.5*
V_{RCa}	21% ± 3.9	16% ± 2.9*
V_{Ab}	42% ± 7.3	35% ± 9.3
Peak Exercise		
V_{RCp}	37% ± 4.8	49% ± 9.3*
V_{RCa}	22% ± 4.2	17% ± 4.0*
V_{Ab}	41% ± 6.7	35% ± 8.5

Table values are mean and standard deviation.* $p \leq 0.05$ when comparing men with women. Table Abbreviations: V_{RCp}, contribution of the pulmonary rib cage compartment; V_{RCa}, contribution of the abdominal ribcage compartment; V_{Ab}, contribution of the abdomen compartment; ET, endurance trained athletes; UT, untrained controls; VT, ventilatory threshold.

At peak exercise, ET had larger ΔV_{CW} (2.46L ± 0.7), ΔV_{RCp} (1.10L ± 0.25), ΔV_{RCa} (0.52L ± 0.13), and ΔV_{Ab} (0.96L ± 0.21) than UT ΔV_{CW} (2.10L ± 0.38), ΔV_{RCp} (0.92L ± 0.21), ΔV_{RCa} (0.52L ± 0.13), and ΔV_{Ab} (0.81L ± 0.25) ($p<0.05$). However the contribution of each compartment did not differ between ET and UT.

Absolute volumes (table 3.4)

Rest and exercise end-inspiratory volumes for the total chest wall (V_{CW},ei) and each compartment (V_{RCp},ei, V_{RCa},ei, V_{Ab},ei) and end-expiratory volumes for the total chest wall (V_{CW},ee) and each compartment (V_{RCp},ee, V_{RCa},ee, V_{Ab},ee) were analyzed.

Table 3.4. Absolute chest wall end-inspiratory and end-expiratory volumes.

	Trained Males		**Untrained Males**		**Trained Females**		**Untrained Females**	
Volume (L)	**Rest**	**EX**	**Rest**	**EX**	**Rest**	**EX**	**Rest**	**EX**
Chest Wall								
V_{CW},ei	23.74 ±3.34	24.85* ±3.05	23.08 ±3.03	24.29* ±3.36	18.78 ±2.06	20.26* ±2.13	18.97 ±1.27	19.67* ±1.48
V_{CW},ee	22.89 ±3.36	22.18* ±3.13	22.43 ±3.02	21.86* ±3.01	**18.27 ±2.07**	**18.01 ±2.05**	18.46 ±1.23	17.89* ±1.39
Pulmonary Ribcage								
V_{RCp},ei	13.69 ±1.94	14.20* ±1.96	**13.02 ±1.63**	**13.54 ±1.93**	11.63 ±1.15	12.38* ±1.13	**12.01 ±1.00**	**12.34 ±1.23**
V_{RCp},ee	13.29 ±1.96	13.06* ±1.87	12.77 ±1.68	12.59* ±1.74	**11.37 ±1.17**	**11.32 ±1.20**	11.73 ±0.94	11.46* ±1.25
Abdominal Ribcage								
V_{RCa},ei	3.89 ±0.65	4.32* ±0.63	3.97 ±0.39	4.35* ±0.48	2.53 ±0.45	2.87* ±0.53	2.02 ±0.22	2.26* ±0.32
V_{RCa},ee	3.72 ±0.72	3.69 ±0.57	3.85 ±0.40	3.83 ±0.41	2.43 ±0.42	2.45 ±0.46	1.95 ±0.21	2.02 ±0.28

Abdomen								
V_{Ab},ei	6.20 ±1.33	6.59* ±1.42	6.10 ±1.85	6.40* ±1.83	4.62 ±0.75	5.01* ±0.95	4.94 ±0.75	5.06* ±0.85
V_{Ab},ee	5.88 ±1.29	5.44* ±1.63	5.82 ± 1.78	5.45* ± 1.63	4.48 ±0.83	4.24* ±0.77	4.78 ±0.72	4.42* ±0.67

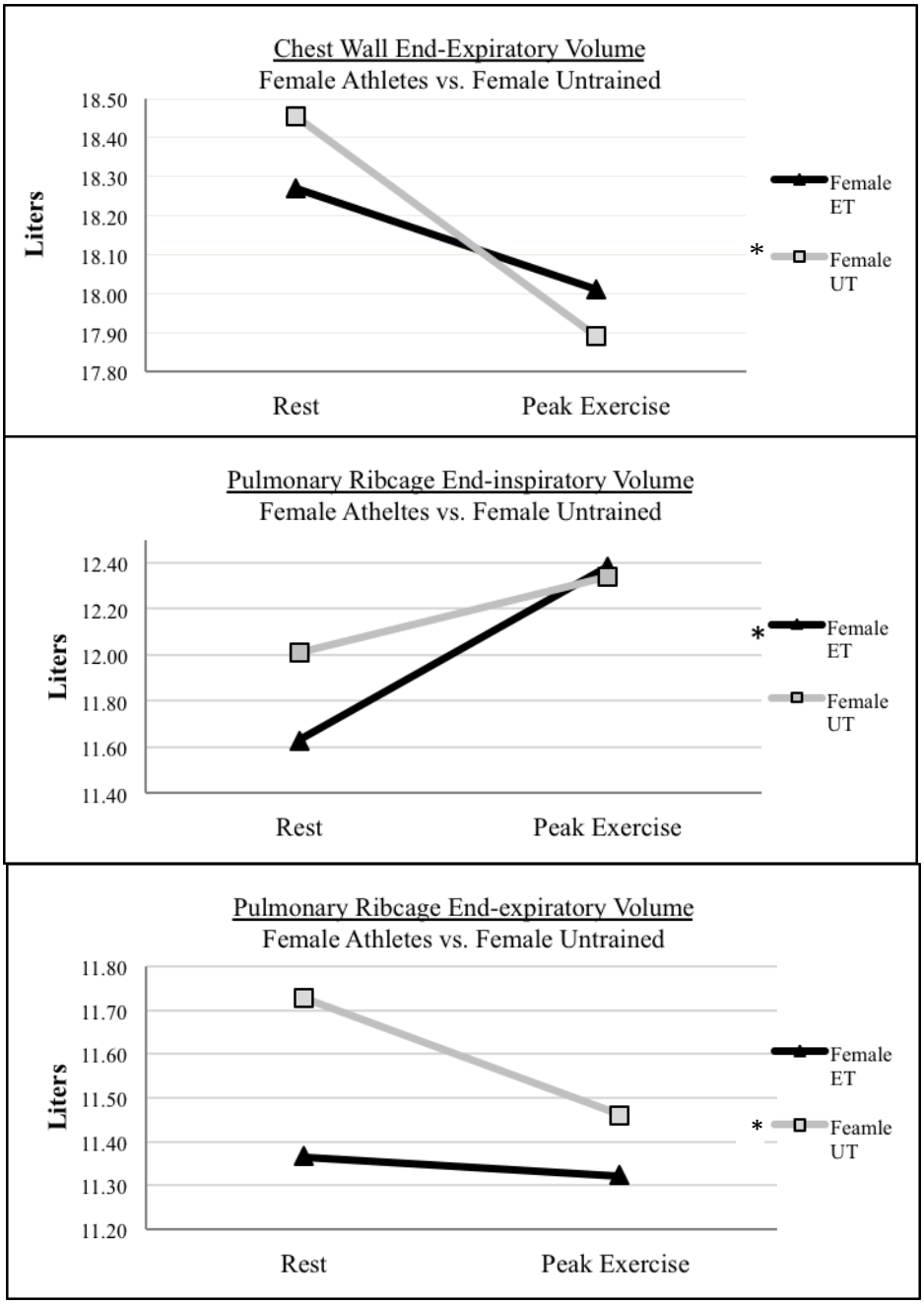
Values are expressed as means and standard deviations.

* significant difference between rest to exercise ($p < 0.05$). Bolded values indicate no significant change in one or two groups and when significant changes in the other groups were present. Abbreviations in table: V_{CW},ei, chest wall absolute end-inspiratory volume; V_{RCp},ei, pulmonary ribcage absolute end-inspiratory volume; V_{RCa},ei, abdominal ribcage absolute end-inspiratory volume; V_{Ab}, abdominal

From rest to peak exercise, all groups significantly increased their V_{CW},ei ($p < 0.05$). Unlike female UT, female ET did not decrease V_{CW},ee (figure 3.2). Female ET and female UT had a different V_{RCp},ei and V_{RCp},ee responses (figure 3.2). Female ET demonstrated significant increases in the V_{RCp},ei ($p<0.05$), female UT did not (figure 3.2). Female UT demonstrated significant decrease in V_{RCp},ee with exercise ($p<0.05$), female ET did not (figure 3.2b). From rest to peak exercise, trained males and trained females increased their V_{RCp},ei ($p<0.05$), but untrained males and untrained females did not (table 3.4). From rest to peak exercise, all groups increased their V_{RCa},ei ($p<0.05$) and V_{Ab},ei ($p<0.05$) (table 3.4).

From rest to peak exercise no group decreased its V_{RCa},ee. All groups significantly decreased V_{Ab},ee ($p<0.05$) (table 3.4).

Figure 3.2. Interaction effects between Female ET and Female UT.



Significance set at $p<0.05$. * Demonstrated significant change from rest to peak exercise in chest wall end-expiratory volume. Abbreviated terms in the table: ET, endurance trained; UT, untrained.

DISCUSSION

This was an observational study of the ventilatory kinematics of endurance male and female athletes compared to untrained controls. Key findings in this study were: with peak exercise, female ET do not significantly decrease V_{CW},ee; female ET are the only group to show no changes to V_{RCp},ee; ET have significant increases in V_{RCp},ei, while UT do not; women (ET and UT) demonstrate different chest wall kinematics from all men; in all subjects, chest wall kinematics were not affected by changes in compartmental volume and did not differ between ET and UT. We predicted that the change in V_{Ab} would be greatest in ET due to athletes' ability to condition their abdominal muscles; however, this was not demonstrated in our population. Therefore we believe that the change in volume from various compartments may be dictated by pressure changes that are not related to muscle conditioning.

The female athletes' inability to decrease V_{CW},ee was an important finding of this study. To our knowledge, this is the first report of a difference in absolute end-expiratory volume during exercise between female athletes, male athletes and untrained males and females. Based on previous work, there are many possible mechanisms to explain these differences between female athletes, male athletes and male and female untrained subjects. Past studies found that female athletes are mechanically constrained because of expiratory flow rates encroaching on the airway flow volume envelope (55). The present study did not evaluate this mechanism but we believe air trapping from the constrained airway flow volume envelope could explain the lack of change in female athletes V_{CW},ee and V_{RCp},ee. Past work has also described possible inter-thoracic pressure differences between female athletes and male athletes (25). The difference in end-expiratory volumes in female athletes may be contributed to subsequent pressure

development during exercise. These theories plus others can be explored in future work to define the mechanism behind our findings.

Increases in the V_{RCp},ei were also significantly different between trained and untrained subjects. Because inhalation is an "active" process, trained subjects' ability to increase end-inspiratory volumes greater than the untrained subjects may be due to better conditioned respiratory muscles. This may also the explanation to how the trained male and female athletes are able to substantially increase their Vt compared to their untrained counterparts.

A notable finding was that trained athletes' kinematics during exercise remained similar to their kinematics at rest, despite approaching maximum ventilation. Kinematics remained constant from rest to maximal exertion in the ET and UT groups, despite the presence of substantially different ventilation, tidal volume, breathing reserve, and oxygen uptake. These findings have never before been reported.

These data demonstrate differences in chest wall kinematics between men and women at rest and during exercise. Irrespective of training status, contributions by the pulmonary ribcage and the abdomen to the total Vt variation were similar in trained and untrained men. In contrast to men, women had greater contributions to the total Vt variation by the pulmonary ribcage than by the abdomen, and this did not vary according to training status. We interpret these data to indicate that women use predominantly thoracic breathing, while men use equal amounts of thoracic and abdominal breathing under both resting and exercise conditions.

Our findings differences in ventilatory kinematics by gender are novel; while two other studies have used OEP to compare breathing variations between genders and only one of these was under exercise conditions (37, 50). Romei et al, studying resting ventilatory kinematics in

various body positions, found similar gender differences as in our study (37). On the other hand, a small study of exercise by Vogiatzis et al found no gender differences in ventilatory kinematics during exercise (50). Vogiatzis et al had a smaller sample size from this study and combined the volumes of the V_{RCp} and V_{RCa} for analysis. By including a larger sample of women and analyzing V_{RCp} and V_{RCa} separately, we were able to demonstrate that the pulmonary ribcage and abdominal wall contributed equally to Vt in men but not in women. To confirm that the difference in analysis could have been the reason for the discrepancies in findings, we combined our V_{RCa} and V_{RCp} and reanalyzed the data. With the V_{RCp} and V_{RCa} combined, found no sex differences were observed.

The variations between women and men may be explained by anatomical differences in the ribcage in addition to the airway differences discussed above. (56). In a study performed by Bellemare et al, female subjects exhibited a greater inspiratory rib cage muscle contribution during resting breathing than males, presumably reflecting an improved mechanical advantage conferred to these muscles by the greater inclination of ribs. The Bellemare study showed a greater inclination of rib in the female rib cages accommodating a greater volume expansion and suggesting a disproportionate growth of the rib cage in females relative to the lung, which would be well suited to accommodate large abdominal volume displacements as in pregnancy (56). Our findings of a greater volume displacement in the pulmonary rib cage in women are in agreement with the findings of Bellemare et al.

To our knowledge, this is the first study analyzing the chest wall volume distribution during exercise in competitive athletes. This is also the largest study to have compared changes in compartmental chest wall kinematics between men and women during intense exercise.

Our study demonstrated no change in the V_{CW} compartmental contribution from rest to maximal exercise. This finding could not have been tested with previous technology, because it was not possible to acquire chest wall volumes during exercise and divide it into individual compartments (30, 33, 57, 58).

Study limitations

An earlier work studied chest wall kinematics in humans during walking by using muscle pressures to analyze the kinematics (6, 48). Unfortunately we could not use this method because our analysis required us to collect metabolic data in the athletes and the untrained individuals at maximum exercise. However, our results support the findings of this previous work, which used OEP along with a measurement of pleural and abdominal pressures to observe men while walking (6, 18, 48).

During our study no EMG data were collected to determine diaphragm or accessory muscle activation. EMG data could further the understanding of the kinematics of breathing in this setting. The use of esophageal and gastric pressures might have given better insight as to why variations between men and women existed, however such measurements cannot be taken during metabolic testing.

CONCLUSION

In summary, we observed that trained individuals increase pulmonary ribcage end-inspiratory volumes with exercise. We also observed an effect of training and genders in that female endurance trained athletes do not decrease chest wall end-expiratory volume. Lastly, women appear to have a greater contribution from their pulmonary ribcage compartment than

men, regardless of exercise or being trained. Future research is needed to determine the mechanism behind the gender and training differences described above.

Chapter IV

Exercise ventilatory mechanics and performance in endurance female athletes with and without exercise expiratory flow limitation

BACKGROUND AND SPECIFIC AIMS

Sex differences between airway size and lung size have been well established (38, 59, 60). Women tend to have smaller large airway cross-sectional areas than men when controlled for lung volume (38). The phenomenon of disproportionately large lung volume to small large airway and tracheobronchial tree diameter is termed dysanapsis (60, 61). Dysanapsis may impact exercise ventilation by contributing to what has been defined as expiratory flow limitation (EFL). EFL is considered when the exercise tidal volume loop exceeds the expiratory curve of the baseline voluntary forced vital capacity maneuver flow volume loop, demonstrating that the participant has achieved or exceeded her expiratory flow volume loop envelope and the baseline limits of her airways (29, 55, 60, 62, 63). It appears that in some individuals, particularly those who are endurance trained, the exercise ventilatory demands and involuntary ventilatory drive cause exercise tidal volume breathing to exceed the individual's resting voluntary forced expiratory boundary. By meeting or exceeding the airway's baseline limits, resistance may increase significantly and lead to increased sheer stress to the airway lumen, inflammation, and increased dyspnea with exercise, along with a potential change in ventilatory mechanics and decrease in exercise performance (64).

The overlapping of exercise tidal volume loops with the baseline forced expiratory curve is considered to be a "flow limitation" because exercise expiratory tidal volume flow rate exceeds the baseline expiratory flow rate. However, the term "flow limitation" implies an

inability to achieve a normal flow rate. Individuals with EFL have been capable of achieving normal flow rates during exercise and, in fact, often achieve supernormal flow rates due to the involuntary ventilatory drive that occurs during-high intensity exercise. What EFL may actually illustrate is a baseline ventilatory inadequacy to accommodate exercise ventilatory demand. Hence, in this usage, the term "flow limitation", describes an inadequate flow reserve, and when flow reserve is decreased or negative (meaning the voluntary maximum flow rate the airways can accommodate has been surpassed during exercise), there may be a limit on exercise duration and performance (26). For continuity sake this paper continued to investigate EFL but further explored other variables that may capture the baseline ventilatory insufficiency to accommodate the exercise ventilatory demands of elite athletes.

The prevalence of exercise EFL caused by dysanapsis in female participants has been reported to be as high as 80% (29, 34). As exercise intensity is increased, active ventilation increases to accommodate metabolic demand, thus tidal volume and airway resistance both rise (57). During exercise, women with dysanapsis have been found to increase resistive force through the large airways from increased tidal volumes. When the resistive force increases to a particular level, the volume of air inhaled may not be fully exhaled before the ventilatory drive stimulates inhalation again, and air begins to be stacked in the lungs The stacking of air in the lungs has been referred to as dynamic hyperinflation (DH) and has been measured by increased end-expiratory lung volume (EEV) and decreased inspiratory capacity (65). In patients with chronic obstructive pulmonary disease (COPD), DH has been associated with increased dyspnea, increased carbon dioxide retention, and decreased inspiratory peak flow with exercise and has been believed to be one of the causes of decreased exercise tolerance in this population (66). Of course, COPD patients have fundamental differences from healthy athletes, but Aliverti et al.

also found that healthy young males with imposed expiratory flow limitation had increased hypercapnia, dyspnea, and decreased peak aerobic capacity and power output (32).

The sheer stress of the high flow resistance from exercise EFL may contribute to increased inflammation in the tracheal lumen in female athletes (67). The increased inflammation in the tracheal lumen has been believed to cause an increase in symptoms similar to those described by persons with exercise-induced asthma (EIA) (68, 69). Anderson et al. has reported that endurance athletes have excessive mucus production and airway edema that may exaggerate the airway narrowing during exercise (70). In addition, Landeau et al. found that female athletes report respiratory symptoms more than male athletes (71). Besides EIA- like symptoms, studies have found participants with EFL to demonstrate increased exertional dyspnea (72, 73). Aliverti et al. theorized that increases in dyspnea could be attributed to increases in EEV from EFL (72). Pelligrino et al. understood that the sensation of dyspnea may alter individuals' breathing patterns, causing greater increases in EEV(65). Therefore, increased dyspnea with exercise may be indicative of EFL in otherwise healthy individuals. Besides dyspnea, values obtained on women by spirometry prior to exercise may indicate a greater potential for exercise EFL. One study investigated the determinants of EFL in women and found that women with EFL have a larger drop in the peak expiratory flow at 25%, 50% and 75% of the flow volume curve (FEF_{25} to FEF_{50} and from FEF_{50} to FEF_{75}) than women who demonstrated no EFL(63). This finding corresponded with work by Rundell et al. who found that FEF_{25-75}% is lower in female ice hockey players with asthma-like symptoms and found that FEF_{25-75}% predicts asthma-like symptoms but not asthma (74). Beyond exercise EFL causing possible increased symptoms, some researchers consider EFL to contribute to decreased exercise tolerance (26).

High peak-exercise capacities in endurance athletes have allowed for greater stress and demand on the ventilatory system and thus increased the chance of exercise EFL, DH and reduced inspiratory capacity (26). Female endurance athletes have been found to have an increased metabolic cost of breathing for a given percentage of maximal aerobic capacity when compared to their male counterparts (75). Guenette et al. attributed the increased resistive work in the female participants to the presence of exercise EFL (75). Increased work of breathing has also been associated with increased ventilatory muscle fatigue that could potentially influence performance (25). Despite the implications of EFL potentially impacting performance, differences between female athletes who experience exercise EFL compared to those who do not have EFL has not been investigated. We asked the question, "Do female endurance athletes who demonstrate exercise EFL have any disadvantage regarding exercise tolerance or capacity when compared to those who do not?" Also, "Does the degree of EFL demonstrated in certain female endurance athletes correlate with a decrease in exercise capacity or level of altered ventilatory mechanics, specifically DH?"

EFL and DH have been linked to increased carbon dioxide retention (76), increased pleural pressure (1), excessive dyspnea (73), and increased abdominal ventilatory work (5) in both patients and healthy individuals. In a study of male athletes where EFL was experimentally induced, the athletes demonstrated DH, decreased slow component oxygen uptake and increased respiratory muscle oxygen utilization (77). The increased oxygen utilization of the respiratory muscles may be representative of the increased work of breathing, which has been correlated with increased oxygen demand and shunting of blood from the periphery (78). Since women have been found to experience EFL more than men, it was not surprising that they would also demonstrate more DH than men (29, 79).

EFL has been found to cause DH above the respiratory compensation point (RCP) (the point where ventilation increases nonlinear to carbon dioxide production) or near maximal exercise (55, 77). Therefore, the intensity of the exercise should be taken into account when testing for exercise EFL and DH. During a race, competitive endurance athletes will go beyond their RCT many times, making them potentially more likely to have DH during competition.

The purpose of this study was to compare the ventilatory mechanics and exercise responses of female endurance athletes (specifically cyclists) with evidence of exercise EFL to those with no evidence of exercise EFL (NEFL) to determine if EFL correlates with changes in ventilatory mechanics and decreases in exercise parameters that may translate into performance decrements.

PRIMARY SPECIFIC AIMS

This study's primary aim was to determine if female endurance athletes with EFL have altered ventilatory mechanics and exercise responses.

Aim 1: Because increased dyspnea has been associated with induced EFL and EFL from disease in previous work, and because symptoms are how clinicians first recognize a problem may be present, our first aim was to determine if participants with exercise EFL had increased dyspnea and DH with exercise.

Hypotheses:

1) The group with exercise EFL would experience greater amounts of dyspnea at maximal exercise compared with female athletes with NEFL.

2) The group with exercise EFL would demonstrate increased DH (defined by increased EEV) during constant load submaximal exercise at a higher intensity (85% maximal work load) than a lower intensity (60% maximal work load) when compared with the NEFL group.

Aim 2: EFL has been considered to limit exercise tolerance. Therefore, we aimed to determine if female endurance athletes with EFL had lower exercise parameters than those with NEFL.

Hypothesis: The participants with EFL would have a lower peak workload and shorter duration at the higher-intensity constant-load test.

Aim 3: Previous literature has correlated EFL with exercise to changes in ventilatory mechanics in males. Therefore, our second aim was to determine if female endurance athletes with EFL also experienced altered ventilatory mechanics from rest to exercise (as defined by differences in compartmental tidal volumes).

Hypothesis: The group with exercise EFL would exhibit altered ventilatory mechanics demonstrated by differences in the tidal volumes of the chest wall compartments (i.e., the pulmonary ribcage, abdominal ribcage and abdomen) and the percent contribution of each compartment to total tidal volume when compared to the NEFL group.

Aim 4: We calculated the percentage of overlap between the exercise tidal volume loops and baseline forced voluntary flow volume loop to find the amount of flow reserve before the limitations of the airways were met. We aimed to determine if variables that had been associated with EFL in previous research could explain a significant amount of the variability in percent of baseline flow volume loop reserve at peak exercise (%FVL reserve) within a regression equation and which, if any, of these variables are independent predictors of %FVL reserve.

Hypothesis:

1) We hypothesized that since mucus production and cough are often observed in endurance athletes and caused by inflammation, these variables would be independent predictors of %FVL reserve.
2) FEF_{25-75}% has been observed in previous literature to be the spirometric variable lower in participants with EFL. Thus we hypothesized that FEF_{25-75}% would be an independent predictor of %FVL reserve.
3) End-tidal carbon dioxide level (measured as $PetCO_2$) has been found to be higher in flow-limited individuals. Therefore, we hypothesized that PetCO2 would be an independent predictors of %FVL reserve.

SECONDARY AIM:

Aim 4: Since spirometry is the gold standard of measuring flow abnormalities, we aimed to determine if values collected during spirometry indicative of flow limitation (i.e.,FEV_1/FVC, FEF_{25-75}, and peak flow) would be significantly different in participants with EFL compared to NEFL.

Hypothesis: Based on previous literature that found a significant difference in the drop of FEF_{25} to FEF_{50} to FEF_{75} in women with EFL compared to NEFL, we hypothesized that the FEF_{25-75} would be lower in the EFL group.

Exploratory Testing

This study also explored the ability to measure tracheal diameter by ultrasound. Previous work examining the relationship between tracheal area and lung volume used invasive measurements or measurements that involve radiation (CT scans) to obtain the tracheal area (59,

60). Recently, tracheal ultrasound was demonstrated to be a viable alternative to the use of trans-esophageal balloon pressures (80) and, unlike CT scans, does not involve radiation. However, adults have increased calcification of the tracheal cartilage rings with age, making ultrasound measurements difficult. Therefore, the diameter of the trachea was measured using ultrasound to determine its feasibility for future work in investigating the effect of dysanapsis on exercise.

Feasibility Aim: To determine the feasibility of using tracheal ultrasound to measure tracheal diameter to examine the role of tracheal anatomy in EFL.

METHODOLOGY

Study Overview

This study was a two-part study design. One aspect was a cross-sectional study design comparing female endurance athletes with or without EFL during exercise. The second was an association study design determining the ventilatory parameters most predictive of exercise EFL. The testing involved two visits to the Human Performance Laboratory in the Vanderbilt Clinic at Columbia University Medical Center-New York Presbyterian Hospital. The first visit served to screen for EFL with exercise, calculate appropriate work rates used for constant load exercise protocol, and collect dyspnea scores with exercise. The second visit involved two submaximal exercise bouts at two intensities.

Informed Consent

All participants provided signed informed consent in accordance to the policies and procedures of the human participants committees of Columbia University Medical Center (CUMC) and Teachers College, Columbia University.

Participants

Recruitment Methods:

Female endurance athletes were recruited from New York City Area cycling and triathlon clubs. Once a woman demonstrated interest, a phone call was placed to explain the protocol and administer a pre-test questionnaire for initial screening to verify eligibility for participation (questionnaire is found in appendix). After the pre-test questionnaire was successfully completed and no exclusion criteria were present, the first study visit appointment was scheduled.

Inclusion Criteria included the following:

- Age 18-50 years

- Women of all races and ethnicities.

- Competitive cyclists and triathletes who had been performing in competitive endurance sports for greater than one year.

- Training >10 hours per week of cycling.

- Participants demonstrating EFL had to have no sign of clinical asthma and normal pulmonary function tests (PFT) to be included in the analysis.

Women were excluded in the presence of the following exclusion criteria:

- Individuals with cardiac, pulmonary (other than exercise induced asthma), neurological or musculoskeletal diseases that limit exercise.

- FEV_1/FVC <70% or the FEV_1 below the lower limits of normal (<75%) for age, sex and body size and/or ≥12% improvement with bronchodilator if FEV_1 decreases with exercise (81).

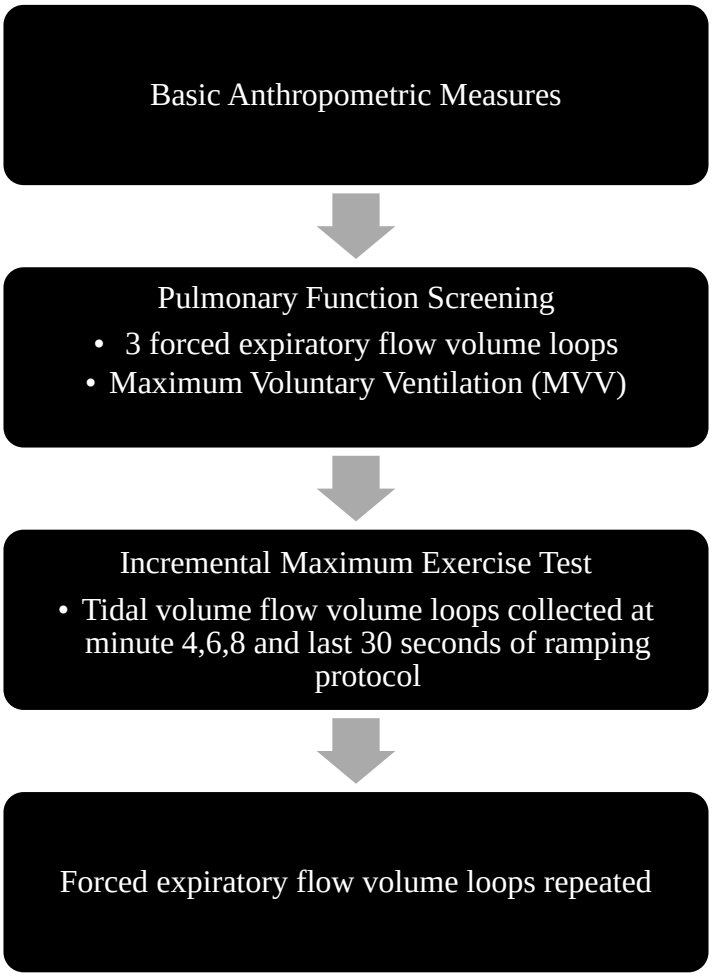
Experimental Design

Two separate laboratory sessions occurred: a one-hour initial visit and a 90-minute follow-up visit, within a week of the initial visit.

The initial visit consisted of a screening that included: (1) a questionnaire to collect information on EIA-like symptoms, (2) training status (miles ridden per week, training hours per

week, number of years competing and racing category), (3) simple anthropometric measurements, and (4) pulmonary function testing to screen for abnormal pulmonary function that exclude participation in the study (FEV_1/FVC <70% predicted). After initial screening took place, participants proceeded with an incremental maximal aerobic capacity exercise test that included expiratory flow-volume curves during the ramping portion of the exercise to detect EFL. The maximum workload achieved during the incremental exercise test was used to set the constant load workloads for the submaximal exercise bouts during session two. Dyspnea (82-84), muscular fatigue (63, 84, 85) and general perceived exertion (63, 84) scores were taken every two minutes at throughout the exercise test. Figure 4.1a demonstrates the workflow of the first visit.

Figure 4.1a. Visit 1

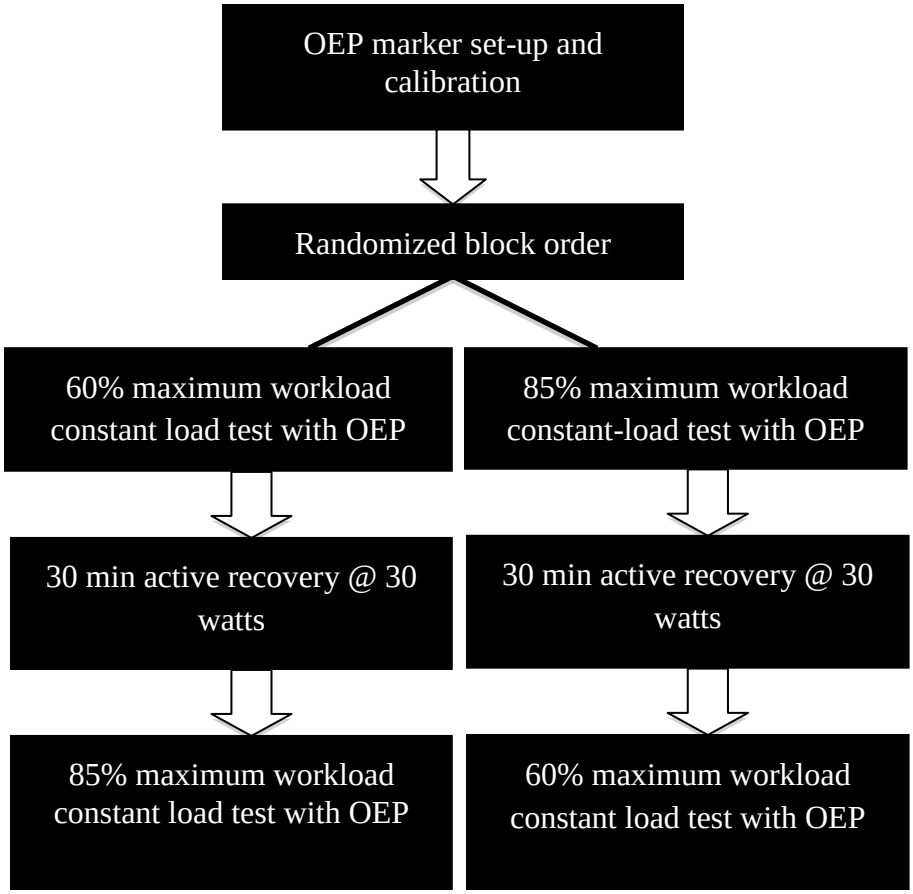


During the initial visit, tracheal ultrasound was performed before or after exercise in a small subset (n=8) of our study to determine the feasibility of using this method to measure tracheal diameter (TD).

The second visit consisted of two constant load exercise protocols with motional analysis testing to calculate chest wall volume changes and ventilatory mechanics. Based on previous research, we believed DH would be likely to occur after the respiratory compensation point (RCP) (29, 77). In cyclists, the RCP has been found to occur at approximately 80% of the peak workload (86). Therefore, we had the participants exercise at a constant load of 60% maximum

workload (well below the RCP) and 85% maximum workload (just above the RCP). Testing order was determined by block randomization. DH was measured by increases in end-expiratory volumes by Optoelectronic plethysmography (OEP) during the constant load protocols. Figure 4.1b demonstrates the workflow of the second visit.

Figure 4.1b. Visit 2



PROCEDURES

Anthropometric measurements

To factor in anatomical variations between participants, anthropometric measurements were taken. Height and weight were measured on a Detecto scale (Detecto, Webb City, MO 64870). Torso length was measured unilaterally from the mid clavicular line to the anterior superior iliac spinea, ribcage circumference was measured at the xiphoid process and the length

of the abdomen was measured unilaterally from the lowest palatable point on the10th rib to the anterior superior spinea. These measurements were selected because they make up the boundaries OEP uses to segregate the various compartments (11).

EIA-like symptoms

If participants answered yes to any of the symptoms on the questionnaire (copy in appendix), we would ask them to rank the severity on a scale of 1-5 (none = 0), with 1 = mild, 2 = moderate, 3 = severe, 4 very severe, 5 = the worst possible wheeze, cough, atopy (allergies), mucus, chest pain, chronic bronchitis, vocal cord discomfort). We then found the average ranking of each symptom (0-5) as well as the frequency of reporting "yes" versus "no" per each group.

Pulmonary Function Testing

Pulmonary function testing was used to screen for exclusion criteria and to measure maximum voluntary ventilation (MVV (L/min) for use in determining the breathing reserve during exercise. Three forced expiratory flow volume loops were performed before and after exercise using a spirometer (Care Fusion, Palm Springs, CA 92262) to acquire forced vital capacity (FVC (L)), forced expiration in one second (FEV_1), forced expiration in one second to forced vital capacity ratio (FEV_1/FVC), and mid expiratory flow rate of the FVC curve (FEF_{25-75}(L/sec)). Acceptable repeatability was considered achieved when the largest and next largest FVC was < 0.150L (87). The loop with the highest FVC was used in analysis. FEF_{25-75} can have up to 20% variability within an individual participant (81). Therefore, the highest and lowest FEF_{25-75} were averaged and that score was used as the FEF_{25-75}.

Exercise Expiratory Flow Limitation (EFL)

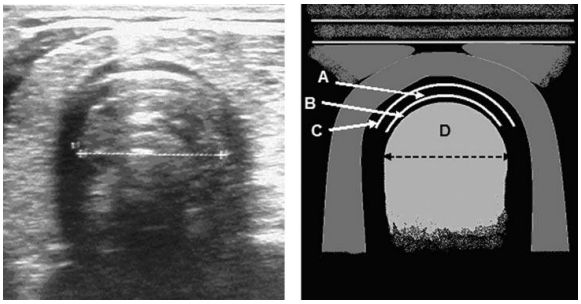
EFL was considered present when the exercise tidal volume flow loop surpassed the pre- or post-exercise expiratory curve of the flow volume loop (88). Participants who overlapped both their pre and post exercise flow volume loops with their exercise flow volume loop were considered to have "definite EFL" and were grouped as (DEFL) (figure 4.4). Participants who only overlapped their pre-exercise flow volume loop but not their post-exercise flow volume loop with their exercise flow volume loop, were considered to have borderline EFL (BEFL) (the term "borderline" was used in reference to the idea that these participants demsontrated an intermediate level of flow volume loop overlap) (figure 4.4). Participants who did not overlap the pre- or post-exercise flow volume loops with their exercise flow volume loop were grouped as NEFL (figure 4.4). Exercise flow volume was measured at minute four, six, eight and during the last thirty seconds of the ramping portion of the incremental exercise test. For analysis, the expiratory flow volume loop was aligned with the largest flow volume loop from pre and post exercise and superimposed on each other (63). The highest flow at any given lung volume was used to represent the boundary of the flow volume envelope (62, 63, 89). The degree of flow volume reserve or lack thereof was quantified by adding the area in pixels (72 x72 dpi, Adobe Photoshop, San Jose, CA 95110) of the exercise flow volume loop to the area overlapping the baseline flow volume loop, then dividing by the area of the baseline flow volume loop. We determined the percentage of forced vital capacity in reserve during exercise by subtracting the area of reserve by one to get percent forced vital capacity reserve (% FVL reserve) (equation below) (example Figure 4.4).

$$\%\ \text{FVL reserve} = \frac{\qquad\qquad}{\qquad\qquad}$$

Tracheal Measurements

The feasibility measurement of tracheal diameter by ultrasound was an exploratory aim. Despite the fact that tracheal cartilage calcification makes viewing the trachea by ultrasound difficult in adults, one study has validated the measurement of tracheal diameter by ultrasound in this population(90). Using the approach of Lakhal et al, ultrasonography was performed breathing at rest by a sonographer using a portable ultrasound machine with a high frequency linear transducer (12Hz) (Philips CX50, Philips, Amsterdam, Netherlands) (90). The sonographer located the vocal cords with the ultrasound and then maneuvered the transducer up the neck along the esophagus towards the participant's head to locate the cricoid arch. When located, measurement was made of the diameter of the cricoid cartilage. Three tracheal diameter measurements were taken and an average of the three measurements was used for analysis. Figure 4.2 from Lakhal et al. demonstrates the area of measurement. Because traditional measurement of tracheal diameter taken by chest radiograph or computed tomography measures the outside diameter of the trachea (91, 92), the ultrasound measured both the inside and outside diameter to determine if the ultrasound measurements were similar to the traditional measurements.

Figure 4.2. Ultrasound of the trachea



Lakhal, K.,Delpace, X., Cottier, J.,Tranquart, F., Sauvagnac, X., Mercier, C., Fusciardi, J., Laffon, M. The feasibility of ultrasound to asses subglottic diameter. Anesthesia & Analgesia. 2007 March; 103 (3): 611-14.

Lakhal et al. The cricoid arch and the air-column, ultrasonography view. Cricoid cartilage is a round hypoechoic structure (the medulla (A)) with hyperechoic edges (the internal (B) and external (C) perichondrium). The air-column (D) appeared hyperechoic and created a posterior

acoustic shadow. The mucosa–air interface, a hypoechoic edge, was easily recognized. The dotted line represents the measured air-column width.

Incremental Maximal Exercise Testing

An incremental maximal aerobic capacity exercise test was performed on an electromagnetically braked cycle ergometer (Viasprint 2900, Care Fusion, Palm Springs, CA 92262) using a 30 watts• min^{-1} ramping protocol to exhaustion. Maximal exercise was considered achieved when heart rate was at predicted maximum (220 (bmp) -age (yrs)) (93), respiratory exchange ratio (RER) was greater than 1.1 (93) and participant could not maintain a cadence of greater than 70 rpm. The testing began with three minutes of resting baseline measurements, followed by a three minutes warm-up at 30 watts· min^{-1}. After warm-up, the resistance was increased at 30 watts·$min^{-1,}$ while the participant kept a pedal cadence of 70-90 rpm (94). Breath-by-breath pulmonary gas exchange was measured using the Vmax Encore Metabolic Cart (Vmax Encore 29, Care Fusion, Palm Springs, CA 92262), which had been calibrated prior to each test according to the manufacturer's instructions. Heart rate (HR) was measured at rest and throughout exercise using a twelve lead electrocardiogram (Cardio V4 MDL37 ECG, Cardiosoft, Houston, TX 77056) and used to calculate oxygen pulse besides heart rate. Blood pressure was also recorded once during rest and every two minutes throughout exercise (95) (Welch Allyn blood pressure cuff, Skaneateles Falls, NY 13153). Metabolic variables collected included oxygen uptake ($o_2$ml·min^{-1}·kg^{-1}), carbon dioxide production (co_2 ml·min^{-1}·kg^{-1}), respiratory exchange ratio (RER), minute ventilation (e (L/min)), breathing reserve (%)(calculated as MVV - e/ MVV x 100) (96), ventilatory equivalent for carbon dioxide (e/ co_2) and oxygen (e / o_2). Ventilatory threshold (VT) and respiratory compensation point (RCP) were identified by the principle investigator and two other exercise physiologists using the modified V-slope

method (calculating a change in the slope of the e line and o_2 line) (97). If there was a discrepancy among the three assessors, the VT was verified by the ventilatory equivalents method (using the e / co_2 and e / o_2) (98). Peak-exercise values were considered the highest values obtained before the participant dropped below the cadence threshold of 70 rpm (93). Peak o_2($ml \cdot min^{-1} \cdot kg^{-1}$) was recorded as the highest 10 sec average of o_2 consumed during the last minute of exercise adapted from the definition in McArdle, Katch and Katch (93).

Ratings of overall perceived exertion (RPE), dyspnea and muscle fatigue were recorded using a modified Borg scale (84) (copy located in the appendix) after every blood pressure. The modified Borg scale is slightly different from the rating of perceived exertion scale. In the modified Borg scale, the word "severe" is used in place of the word "hard". To keep participants from becoming confused between scales we used the modified Borg scale for rating dyspnea, muscle fatigue and over all perceived exertion. The use of the modified Borg scale for measuring both dyspnea and muscle fatigue has been performed in previous studies (99, 100).

Constant Load Submaximal Exercise Tests

Two constant load submaximal exercise tests at two separate workloads were performed during the second laboratory visit. The order of the two tests was determined using a randomized block design and separated by thirty minutes of active recovery at 30 watts• min^{-1} to minimize the effect of the prior exercise bout on the latter (101).

The constant load exercise test began with a three minute warm-up of unloaded pedaling on the cycle ergometer (Viasprint 2900, Care Fusion, Palm Springs, CA 92262). After the three minutes of warm-up, the predetermined load (described below) was applied to the cycle ergometer. For all constant-load tests, participants were asked to sustain the selected work rate

for 10 minutes or until volitional fatigue. Participants were instructed to maintain an even cadence of 70-90 rpm during all testing (101). If at any time the participant decreased her cadence below 70 rpm and could not return to 70 rpm despite being encouraged to do so, the test was terminated. If the participant could not complete the 10 minutes of constant load exercise, the total time completed was recorded (102). The two constant-load tests were at 60% and 85% maximum workload to determine if a higher intensity of exercise elicited increases in EEV. Eighty-five percent of the maximum workload was a workload above all participants' RCP. OEP was measured during each constant-load test (method of measuring OEP detailed below).

Trunk position relative to hip angle may contribute to changes in breathing mechanics (37). Therefore, the torso angle was also measured at rest and at 30 seconds before the end of the constant load exercise tests. Participants were instructed to remain upright during tests and reminded to keep their chests upright while pedaling to attempt to prevent body angle changes. Torso angle was defined as the degrees from vertical of the line connecting the C7 marker on the neck and the base of the bicycle saddle. A protractor and reference tool located on the three-dimensional reconstruction of the chest wall in the OEP software were used to measure the torso angle.

Optoelectronic Plethysmography (OEP)

Advances in motion analysis technology have allowed researchers to better non-invasively measure exercise ventilatory mechanics. This study used a motion analysis system called Optoelectronic Plethysmography (OEP) (BTS, Bioengineering, Milan Italy). OEP segregates the chest wall into its three main components: the pulmonary ribcage (clavicular line to the xiphoid apophysis), abdominal ribcage (xiphoid apophysis to base of costal margin) and

the abdomen (tip of the processus xiphoideus and costal margin to the anterior superior iliac spines) (11). Changes in chest wall volumes from each of these compartments can indicate an alteration in thoracoabdominal mechanics (11). The OEP set-up consisted of placing 89 reflective markers on the participant's chest, abdomen and back in order to map the participant's trunk. The markers followed a grid using anatomical references as a guide (36). Eight infrared cameras surrounded the participant, achieving 360 of marker visibility. They recorded the movement of the markers to calculate volume changes (11). This technique has been shown to be valid in both healthy and clinical populations at rest and during maximal exercise (21, 48-51).

Once the markers were placed on the participant, one minute of resting data were collected. After the first minute of rest, participants continued to have OEP data collected throughout both constant load protocols. During these protocols participants cycled with their hands on handlebars placed along the sides of the cycle ergometer so that their limbs would not interfere with the marker visibility.

Ventilatory mechanics were measured by changes in chest wall compartment tidal volumes (L) (V_{RCp}, V_{RCa}, V_{Ab}) and percent change in volume of each compartment to the total chest wall volume ($\%V_{RCp}$, $\%V_{RCa}$, $\%V_{Ab}$) (36, 79) at rest and during constant-load testing. We calculated dynamic hyperinflation (DH) during exercise by the measurement of the absolute end expiratory compartmental chest wall volumes (EEV) at rest and throughout exercise using OEP. Normal response to exercise is a decrease in end-expiratory volume as tidal volumes increase (103), whereas an increase in end expiratory volume from early exercise to end of exercise is indicative of DH (50, 104). We measured EEV throughout the constant-load test and subtracted the lowest EEV from the EEV during the last 30 seconds of the constant load protocol to determine if EEV increased with exercise.

Statistical Analysis

All statistical analyses were performed using SPSS 15.0 (SPSS, Chicago, IL USA). Descriptive statistics were reported as means and standard deviations. Significance was set *a priori* at $p<0.05$ for all statistical analyses. All variables were tested for normality using a Kolmogorov-Smimov with Lilliefors significance correction. Differences in the demographic, anthropometric, symptoms and exercise parameters between our three groups (DEFL, BEFL and NEFL) were tested using a one-way ANOVA with post hoc Bonferroni correction. Differences between the frequencies of a symptom being reported in each group were tested using Pearson's Chi-square test. Training time and racing status were not normally distributed; therefore differences between groups in training and racing status were tested by a Kruskall Wallis non-parametric test. We hypothesized that the participants with EFL would have greater dyspnea than NEFL. To test this hypothesized difference we used a Mann Whitney U test with significance set at $p<0.05$.

We also hypothesized that the participants with EFL would have increased EEV compared to the participants with NEFL and altered ventilatory mechanics with exercise. Repeated measure ANOVAs with two between subject factors (EFL or NEFL) and one within factor (either % compartmental contribution or EEV) with 3 levels (pulmonary ribcage, abdominal ribcage, abdominals) were used to test our hypotheses. A test of within subjects contrast investigated the differences between resting, 60% max watts and 85% max watts constant-load tests for EEV and 60% max watts and 85% max watts constant-load tests for kinematics. Statistical significance was set *a priori* at $p \leq 0.05$ for all analyses. Mauchly's test of sphericity was performed to correct for variability in error of repeated measures and the Huynh-Feldt correction was used to correct for variability in experimental error over time.

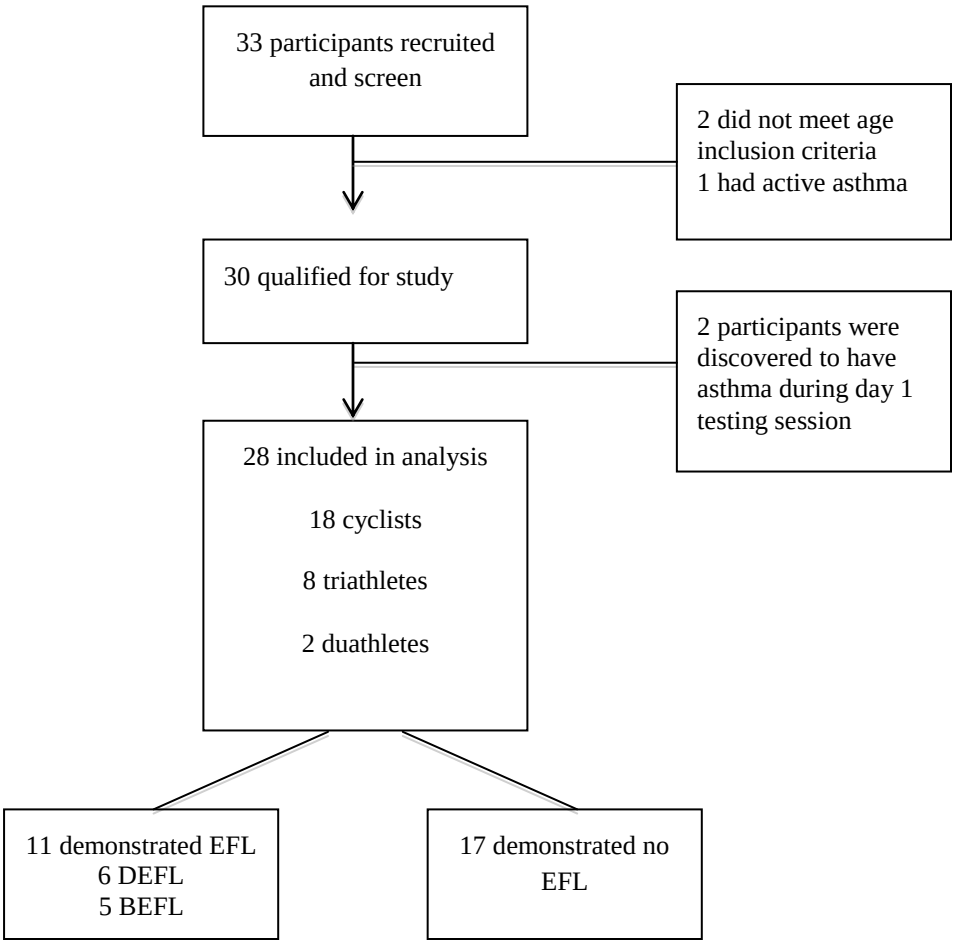
To determine if parameters previously described in other work to be associated with EFL could significantly explain the amount of variability in %FVL reserve, we performed a linear regression including history of mucus production (0-5 rating), FEF_{25-75}%, $PetCO_2$ and $\%V_{RCp}$. We tested covariance between these parameters using a Pearson's correlation test.

RESULTS

Participants Characteristics

Thirty-three female endurance athletes were screened, thirty qualified for testing, two participants were found to meet the clinical criteria of asthma upon testing and were not included in the analysis (their results can be found in table 4.7) and four participants reported a past history of albuterol use but had normal pulmonary function and were included (all in the NEFL group). Figure 4.3 depicts recruitment and inclusion breakdown of participants. Thus twenty-eight women were included in the final analysis.

Figure 4.3 Diagram of participant break down

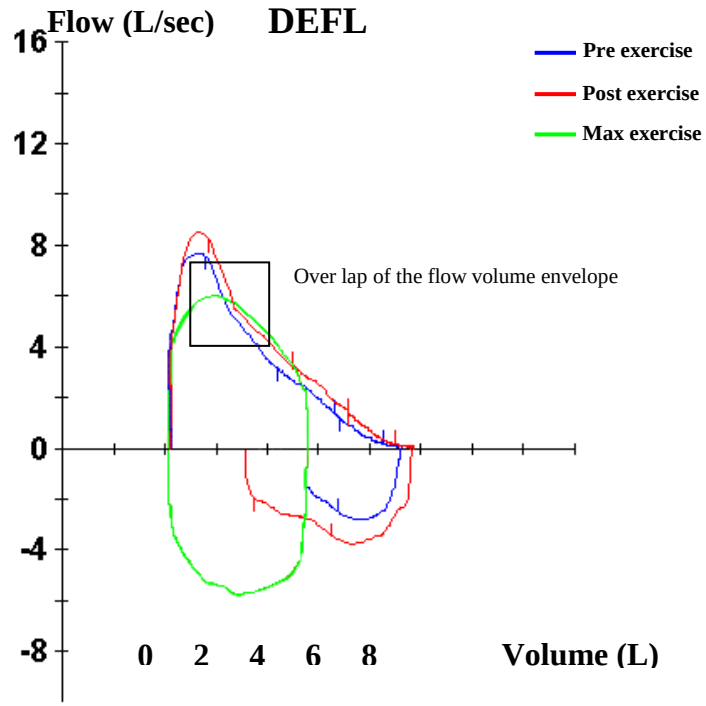


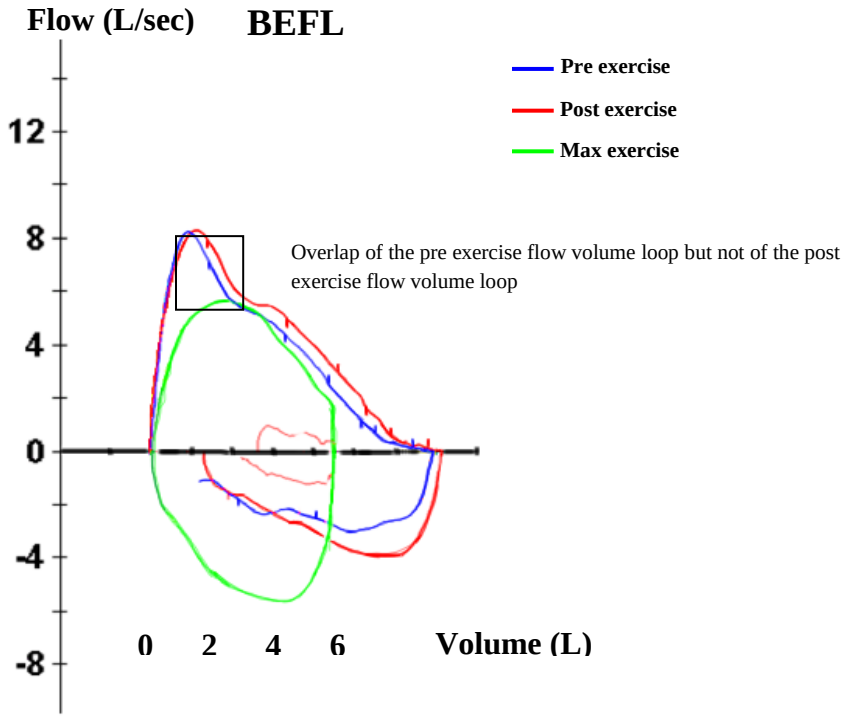
Exercise Expiratory Flow Limitation (EFL)

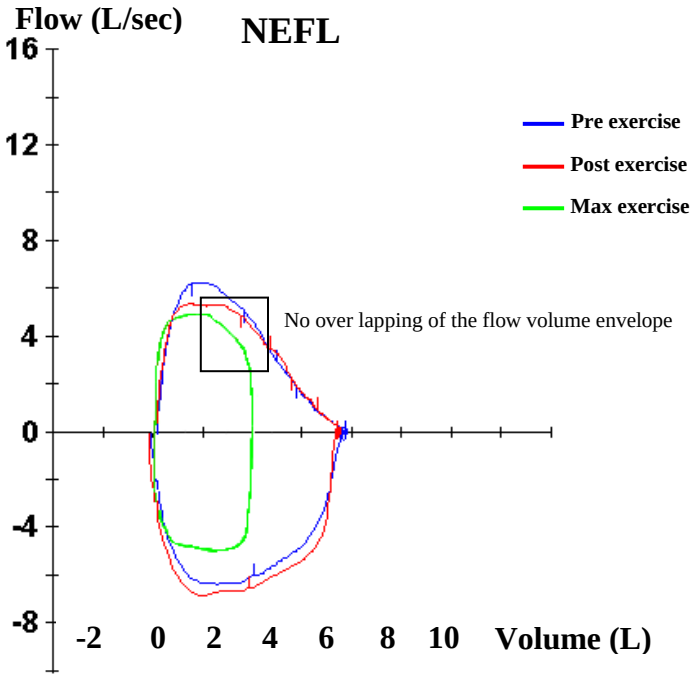
Out of the twenty-eight total participants, six participants demonstrated an overlap of both the pre-exercise flow volume loop and post-exercise loop and therefore comprised our definite flow limitation group (DEFL). Five participants demonstrated overlapping of the pre-exercise flow volume loop at peak exercise but not the post exercise loop, were considered to have borderline flow limitation and comprised our borderline flow limitation group (BEFL). Seventeen subjects demonstrated no overlap of pre- or post-exercise flow volume loop and

therefore comprised our no exercise expiratory flow limitation group (NEFL). As described in the methods, to express this range of flow volume loop reserve and overlap between the peak-exercise flow volume loop and the baseline flow volume loop we developed a continuous variable and labeled this variable percent flow volume loop reserve (%FVL reserve). The participants with both pre- and post-exercise flow volume overlap (DEFL n=6) had 22± 9% FVL reserve at peak exercise. The participants with only pre-exercise flow volume overlap (BEFL n=5) had 33± 10% FVL reserve at peak exercise, and the participants with no flow overlap of pre- or post-exercise flow volume loop (NEFL n=17) had 46± 15% FVL reserve at peak exercise. Therefore, the DEFL group overlapped 78% of their baseline flow volume loop at peak exercise (or had 22% reserve as shown above) whereas the NEFL group still had almost 50% of their baseline flow volume loop in reserve at peak exercise. The overlapping of the baseline, post-exercise and peak-exercise flow volume loops for a representative participant in the DEFL group, BEFL group and NEFL group are shown in figure 4.4.

Figure 4.4 Representative participants with Definite Expiratory Flow Limitation (DEFL), Borderline Expiratory Flow Limitation (BEFL) and with no expiratory flow limitation (NEFL)







Demographics and anthropometric measurements are shown in Table 4.1. Baseline anthropometric measurements were not significantly different between groups.

Table 4.1 Demographics, anthropometric measurements and training and racing

Parameter	DEFL (n=6)	BEFL (n=5)	NEFL (n=17)	P value
Age (yrs)	37 ± 6	36 ± 10	33 ± 8	0.463
Height (cm)	171 ± 5	164 ± 8	165 ± 7	0.108
Weight (Kg)	63 ± 4	57 ± 6	60 ± 6	0.276
BMI ($kg \cdot m^{-1}$)	21 ± 1	21 ± 3	22 ± 2	0.362
Torso length (cm)	47 ± 2	43 ± 4	44 ± 3	0.133
10th rib to SIS (cm)	16 ± 2	16 ± 2	15 ± 3	0.932
Ribcage Circumference (cm)	77 ± 3	77 ± 7	78 ± 4	0.293
Racing Experience (yrs)	5 ± 5	4 ± 3	4 ± 5	0.843
Hours per week of cycling	13 ± 3	11 ± 1	12 ± 4	0.697
Miles per week of cycling	156 ± 72	190 ± 26	157 ± 72	0.606

BMI- Body Mass Index; SIS –Supra iliac spine.
Values are means and standard deviations. *Significance set at $p \leq 0.05$. DEFL: Participants that demonstrated overlapping of their peak-exercise flow volume loop with their pre- and post-exercise flow volume loops; BEFL: Participants that demonstrated overlapping of their peak-exercise flow volume loop with their pre-exercise flow volume loop but not their post-exercise flow volume loop; NEFL: Participants that did not demonstrate any overlapping of their peak-exercise flow volume loop with their pre- and post-exercise flow volume loops.

Participants' training and racing experience is described in table 4.1. There were no significant differences in training and racing experience between groups. There were no statistical differences between the groups in training, competition level and the percentage of cyclists and non-cyclists.

Symptoms

Likewise, there were no significant differences between EIA-like symptoms between any of the groups (table 4.2). EIA-like symptoms did not correlate with %FVL reserve.

Table 4.2 Comparison of Exercise induced Asthma like symptoms in daily life

	DEFL (n=6)		BEFL (n=5)		NEFL (n=17)		
Parameter	Average	Frequency	Average	Frequency	Average	Frequency	P value
Wheeze	1 ± 2	33%	0 ± 0	0%	1 ± 2	30%	0.484
Cough	1 ± 1	33%	0 ± 0	0%	1 ± 1	18%	0.571
Atopy	0 ± 1	17%	0 ± 0	0%	1 ± 1	24%	0.631
Mucus	1 ± 1	33%	0 ± 0	0%	0 ± 0	6%	0.081
Bronchitis	0 ± 0	0%	0 ± 0	0%	0 ± 1	12%	0.633

Values are means and standard deviations. Rated 0-5, 0 being none and 5 being very severe. *Significance set at $p \leq 0.05$. DEFL: Participants that demonstrated overlapping of their peak-exercise flow volume loop with their pre- and post-exercise flow volume loops; BEFL: Participants that demonstrated overlapping of their peak exercise flow volume loop with their pre-exercise flow volume loop but not their post-exercise flow volume loop; NEFL: Participants that did not demonstrate any overlapping of their peak-exercise flow volume loop with their pre- and post-exercise flow volume loops.

Spirometry

Spirometry results are shown in table 4.3. All participants included in the study had "normal" results on all of the spirometry tests and on average were slightly above 100% of the predicted normal for age, sex and height. When compared with the NEFL group, participants with DEFL and BEFL had significantly lower FEV_1/FVC ratio, FEV_1/FVC ratio % predicted, FEF_{25-75} (L) and $FEF_{25-75\%}$ predicted (table 4.3). The amount of change in $FEF_{25-75\%}$ predicted from pre to post exercise significantly correlated with %FVL reserve ($p=0.023$) and was an independent predictor of %FVL ($p=0.02$).

Table 4.3. Results of Spirometry Tests

Parameter **Pre Exercise**	DEFL (n=6)	BEFL (n=5)	NEFL (n=17)	P value	P value (DEFL vs. BEFL)	P value (DEFL vs. NEFL)	P value (BEFL vs. NEFL)
FVC (L)	4.31 ± 0.43	4.05 ± 0.50	4.10 ± 0.63	0.693			
FVC % predicted	109 ± 14	109 ± 8	106 ± 12	0.862			
FEV_1 (L)	3.29 ± 0.18	3.10 ± 0.51	3.45 ±0.54	0.370			
FEV_1 % predicted	105 ± 7	109 ± 9	112 ± 13	0.355			
MVV (L/min)	122 ± 9	125 ± 7	129 ± 16	0.577			
MVV % predicted	112 ± 11	114 ± 12	113 ± 14	0.958			
FEV_1/FVC ratio$^{\Delta}$ (%)	77 ± 5	79 ± 3	83± 4	0.003*	0.418	0.003	0.011
FEV_1/FVC ratio$^{\Delta}$ % predicted	99 ± 6	102 ± 3	107 ± 5	0.002*	0.444	0.022	0.046
FEF_{25-75} (L)	2.92 ± 0.41	3.10 ± 0.43	3.86 ± 0.75	0.008*	0.502	0.001	0.014
FEF_{25-75}% predicted	84 ± 10	92 ± 16	110 ± 18	0.004*	0.350	<0.001	0.068
Peak flow (l/sec)	7.1 ± 1.3	8.2 ± 1.7	7.4 ± 1.4	0.411			
Peak flow (%)	106 ± 21	128 ± 27	113 ± 19	0.195			
Post Exercise							
FVC (L)	4.44 ± 0.40	4.05 ± 0.42	3.99 ± 0.59	0.221			
FVC % predicted	110 ± 12	109 ± 12	104 ± 13	0.413			
FEV_1 (L)	3.66 ± 0.38	3.37 ± 0.39	3.46 ± 0.60	0.663			
FEV_1 % predicted	112 ± 10	115 ± 8	113 ± 14	0.885			
FEV_1/FVC ratio$^{\Delta}$ (%)	79 ± 4	84 ± 5	87 ± 5	0.006*	0.124	0.002	0.250
FEF_{25-75} (L)	3.22 ± 0.47	3.46 ± 0.69	4.08 ± 0.91	0.064			
FEF_{25-75}% predicted	92 ± 11	116 ± 20	104 ± 20	0.027*	0.144	0.002	0.150
Change in FVC (%) predicted from pre to post exercise	3.33 ± 2.33	0.40 ± 3.05	-2.59 ± 3.69	0.003*	0.119	0.002	0.105
Change in FEV_1 (%) predicted from pre to post exercise	6.50 ± 3.51	6.20 ± 5.40	0.65 ± 4.61	0.012*	0.918	0.008	0.083
Change in FEV_1/FVC ratio (%) from pre to post exercise	2 ± 3	5 ± 5	3 ± 4	0.269			
Change in FEF_{25-75}% predicted from pre to post exercise	11 ± 9	19 ± 16	7 ± 16	0.286	0.271	0.01	0.149

Values are means± standard deviations. *Significance set at $p \leq 0.05$. DEFL: Participants that demonstrated overlapping of their peak-exercise flow volume loop with their pre- and post-exercise flow volume loops; BEFL: Participants that demonstrated overlapping of their peak-exercise flow volume loop with their pre-exercise flow volume loop but not their post-exercise flow volume loop; NEFL: Participants that did not demonstrate any overlapping of their peak-exercise flow volume loop with their pre- and post-exercise flow volume loops.
% predicted- percent predicted normalized for height, age, gender and race.
FVC- Forced vital capacity; FEV_1- forced expiration in one second; FEF 25-75%- peak expiratory flow between 25% and 75% of FVC; MVV- Maximum voluntary ventilation. Δ Average reference norm =78 ±1%.

Exercise Tests

After the resting measurements were completed, all participants completed a maximal aerobic capacity exercise test. All participants met the criteria of maximal exercise as described in the methods. Table 4.4 describes the responses at peak exercise. There were no significant differences between the groups. However, end-tidal carbon dioxide pressure ($PetCO_2$) was an independent predictor of %FVL reserve (p=0.005).

Table 4.4 Exercise responses during incremental exercise test

	Peak Exercise			
Parameter	DEFL (n=6)	BEFL (n=5)	NEFL (n=17)	P value
e (L/min)	123.8 ± 9.1	117.2 ± 12.7	121.1 ± 20.2	0.961
Breathing reserve (%) $^{\Delta}$	-2 ± 5	7 ± 10	6 ± 11	0.142
Dead space ventilation (V_D/V_T)	0.08 ± 0.02	0.108 ± 0.02	0.11 ± 0.03	0.134
Pet CO_2 (mmHg)	36.9 ± 1.3	37.4 ± 3.9	36.2 ± 3.8	0.314
e/ co_2	29 ± 1	30 ± 3	31 ± 4	0.280
e / o_2	31 ± 3	33 ± 3	35 ± 5	0.129
Peak o_2 ($ml \cdot min^{-1} \cdot kg^{-1}$)	59.6 ± 6.0	59.9 ± 9.5	56.2 ± 6.8	0.210
% predicted o_2	175 ± 25	162 ± 29	156 ± 25	0.188
Heart rate (bpm)	176 ± 8	173 ± 10	179 ± 12	0.291
Power output ($watts \cdot min^{-1}$)	317 ± 37	299 ± 38	292 ± 34	0.246
% predicted power output	211 ± 30	219 ± 28	206 ± 31	0.491
Power output· body weight	5.07 ± 0.54	5.29 ± 0.78	4.88 ± 0.67	0.269
O_2 pulse % predicted	188 ± 21	180 ± 24	193 ± 66	0.591
RER	1.12 ±0.02	1.16 ± 0.05	1.17 ± 0.04	0.076
Dyspnea Score	8 ± 2	8 ± 1	8 ± 2	0.611
Muscle fatigue Score	9 ± 2	7 ± 2	8 ± 2	0.690
RPE (max)	9 ± 2	8 ± 1	8 ± 2	0.392
Ventilatory Threshold (VT)				
VT o_2($ml \cdot min^{-1} \cdot kg^{-1}$)	48.1 ± 4.8	46.5 ± 5.8	42.7 ± 6.7	0.456

VT Power output (watts·min^{-1})	234 ± 28	212 ± 30	206 ± 25	0.123
Respiratory Compensation Point				
RCP o_2(ml·min^{-1}·kg^{-1})	54.8 ± 6.8	54.6 ± 9.2	50.9 ± 7.7	0.206
RCP Power output (watts·min^{-1})	266 ± 34	253 ± 33	256 ± 33	0.722

Values are means± standard deviations. *Significance set at p≤ 0.05. DEFL: Participants that demonstrated overlapping of their peak-exercise flow volume loop with their pre- and post-exercise flow volume loops; BEFL: Participants that demonstrated overlapping of their peak-exercise flow volume loop with their pre-exercise flow volume loop but not their post-exercise flow volume loop; NEFL: Participants that did not demonstrate any overlapping of their peak-exercise flow volume loop with their pre- and post-exercise flow volume loops. RPE – rating of perceived exertion; e- minute ventilation; Breathing reserve (%)- percentage of breathing reserve at maximal exercise, $^{\Delta}$calculated as breathing reserve = ((MVV- e $_{max}$)/MVV)*100); $PetCO_2$- End-tidal carbon dioxide; e / co_2 - breathing efficiency, minute ventilation per liter of carbon dioxide; e/ o_2- breathing efficiency, minute ventilation per liter of oxygen consumed; Peak o_2- highest oxygen consumption; % pred o_2- percent of normal predicted for the maximal aerobic capacity; Max HR- highest maximum heart rate; O_2 pulse % pred- percent predicted normal for the oxygen pulse. RER- respiratory exchange ratio.

The results of the submaximal steady workload tests did not reveal any significant differences between groups in power output, exercise time or torso angle at the 60% or 85% maximal workload constant-load test between groups.

Table 4.5 Submaximal constant load power and time achieved

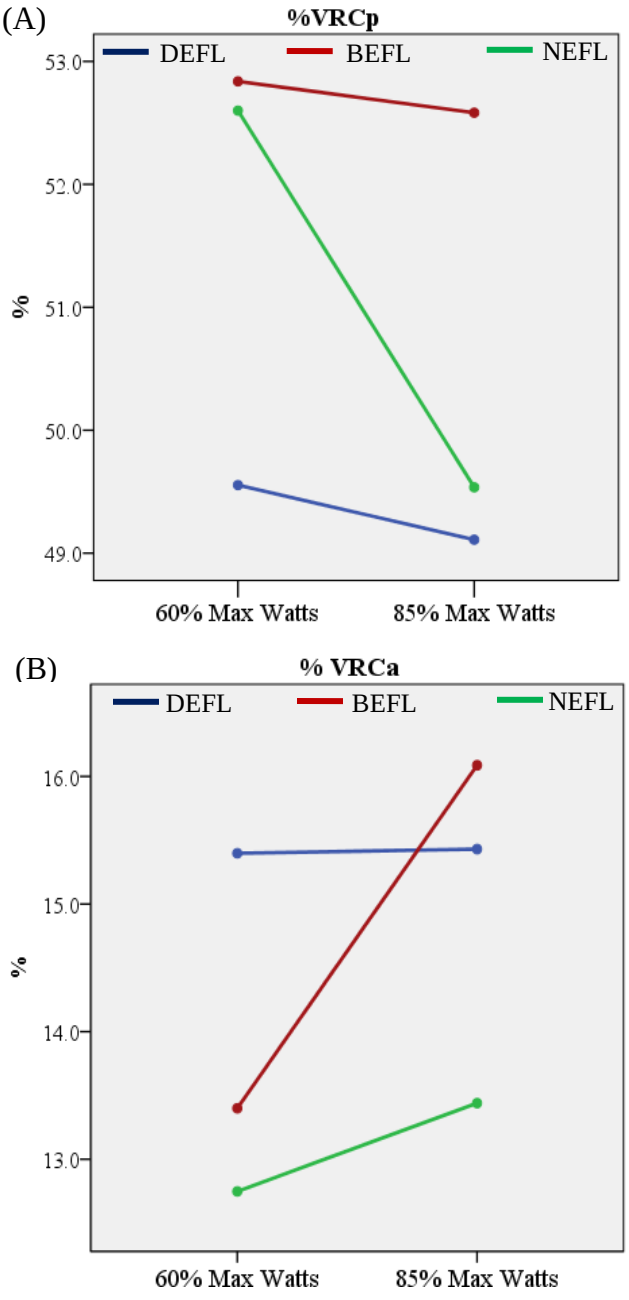
	60% maximal workload constant load				85% maximal workload constant load			
	DEFL (n=6)	BEFL (n=5)	NEFL (n=17)	P value	DEFL (n=6)	BEFL (n=5)	NEFL (n=17)	P value
Watts ·min^{-1}	190 ± 22	180 ± 24	175 ± 20	0.213	269 ± 32	254 ± 32	240 ± 98	0.275
Duration work load (seconds)	600 ± 0	600 ± 0	600 ± 0	1.0	240 ± 98	179 ± 53	172 ± 58	0.175
ΔTorso angle (degrees)	6.12 ± 4.2	4.30 ± 10.70	3.88 ± 6.38	0.557	19.62 ± 6.49	12.54 ± 10.47	14.43 ± 9.45	0.581

ΔTorso angle = the change in torso angle from rest to last 30 seconds of exercise. Values are means± standard deviations. *Significance set at p≤ 0.05. DEFL: Participants that demonstrated overlapping of their peak-exercise flow volume loop with their pre- and post-exercise flow volume loops; BEFL: Participants that demonstrated overlapping of their peak-exercise flow volume loop with their pre- exercise flow volume loop but not their post-exercise flow volume loop; NEFL: Participants that did not demonstrate any overlapping of their peak-exercise flow volume loop with their pre- and post-exercise flow volume loops.

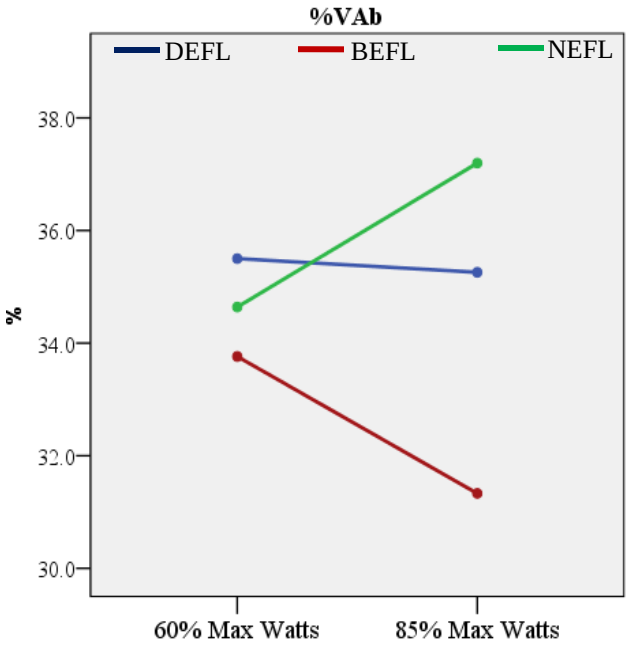
Ventilatory Mechanics during Submaximal Exercise Tests by OEP

Figure 4.5 presents the ventilatory mechanics measured by OEP during the submaximal exercise bouts. In two participants the adhesiveness of the markers was lost due to heavy perspiration during the 85% constant workload, therefore these participants' data were not included in the analysis of the ventilatory mechanics at 85% maximum workload.

Figure 4.5 Interaction effect of test by group in ventilatory mechanics during constant-load testing



(C)



$\%V_{RCp}$; percent pulmonary ribcage contribution to total tidal volume, $\%V_{RCa}$; percent abdominal ribcage contribution to total tidal volume, $\%V_{Ab}$; percent abdomen contribution to total tidal volume.

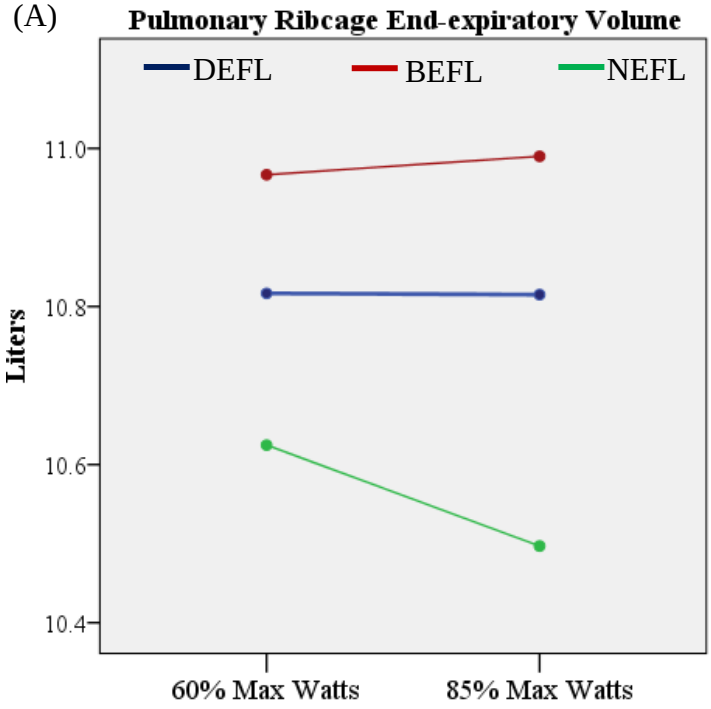
During the constant-load tests, there was no significant interaction effect in the percent pulmonary ribcage contribution to total tidal volume ($\%V_{RCp}$) between workload level and group (Figure 4.5, A). There was significant interaction effect between test level and group in the percent abdominal ribcage contribution to total tidal volume ($\%V_{RCa}$) (p=0.045) (Figure 4.5, B) (p=0.045), and in the percent abdomen contribution to total tidal volume ($\%V_{Ab}$) (p=0.049) (Figure 4.5, C).

Dynamic hyperinflation

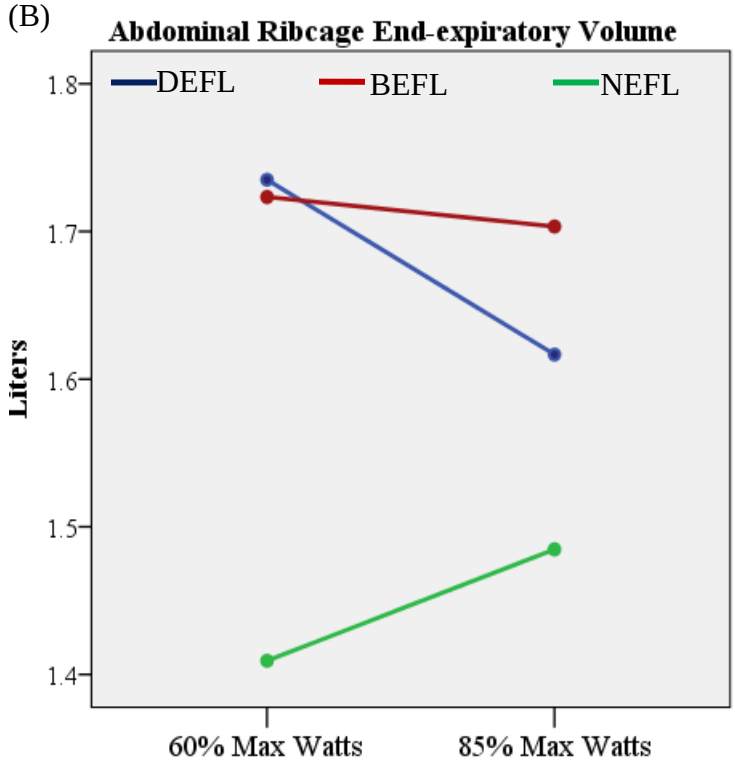
There was no significant interaction effect between group and intensity in participants' pulmonary ribcage EEV (p=0.771) (Figure 4.6, A) or abdominal EEV (p=0.113) (Figure 4.6, C). There was a significant interaction effect between constant-load test and group in participants' abdominal ribcage EEV (p=0.003) (Figure 4.6, B).

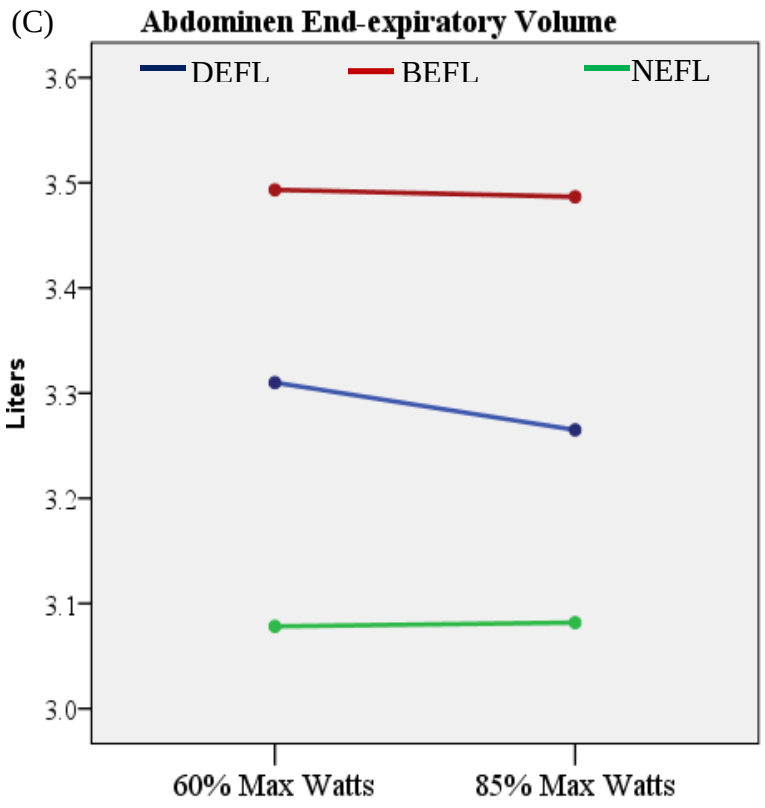
Figure 4.6 Interaction effect of test level by group in end-expiratory volumes

(A)


Pulmonary Ribcage End-expiratory Volume
DEFL
BEFL
NEFL
11.0
10.8
10.6
10.4
Liters
60% Max Watts
85% Max Watts

(B)


Abdominal Ribcage End-expiratory Volume
DEFL
BEFL
NEFL
1.8
1.7
1.6
1.5
1.4
Liters
60% Max Watts
85% Max Watts



Percent Flow Volume Loop Reserve

We constructed a model using the change in $FEF_{25-75\%}$ predicted, report of excessive mucus production with exercise, increases in $PetCO_2$, and decreased percentage of pulmonary ribcage tidal volume to total tidal volume at the 85% maximum workload constant-load test ($\%V_{RCp}$). Our model could account for 71.6 of the variance in %FVL reserve (p=0.002) (Figure 4.7 and Table 4.6). Of that value change in $FEF_{25-75\%}$ predicted from pre to post exercise was an independent predictor of %FVL reserve (p=0.010). Self reported excessive mucus production with exercise was also an independent predictor of %FVL reserve (0.014). Lastly, increased $PetCO_2$ at peak exercise was also an independent predictor of %FVL reserve (p=0.033). The $\%V_{RCp}$ was not an independent predictor of %FVL reserve (p=0.071), however $\%V_{RCp}$ did add to

the R value when included in the equation, and therefore we felt it worth including in the equation. None of these variables were covariates.

Table 4.6 Regression Model Summary, ANOVA and Coefficients

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.716[a]	.512	.427	.12039

a. Predictors: (Constant), VRCp (%), FEF25-75%, Mucus, PetCO_2 (mmHg)

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	.350	4	.087	6.036	.002[b]
	Residual	.333	23	.014		
	Total	.683	27			

a. Dependent Variable: %FVL reserve

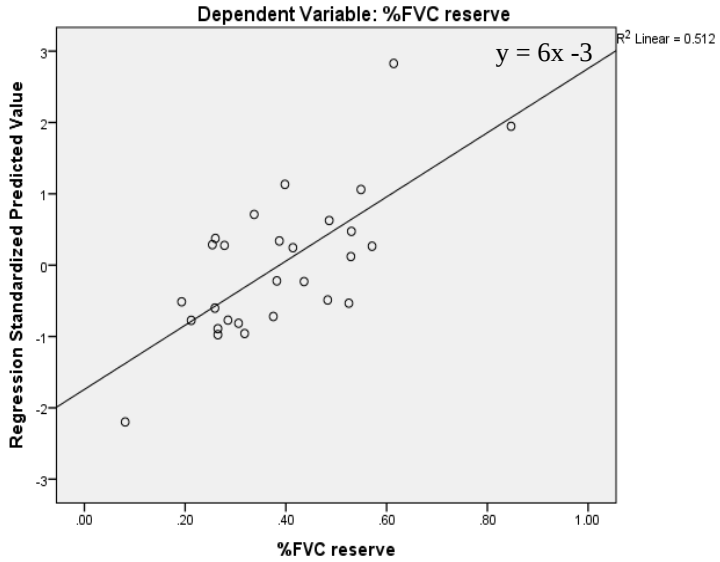
b. Predictors: (Constant), VRCp (%), FEF25-75%, Mucus, Pet CO_2 (mmHg)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.139	.320		.436	.667
	FEF25-75%	-.004	.002	-.414	-2.825	.010
	Mucus	-.140	.053	-.396	-2.651	.014
	Pet CO_2 (mmHg)	.016	.007	.342	2.272	.033
	VRCp (%)	-.005	.003	-.287	-1.883	.072

a. Dependent Variable: %FVC reserve

Figure 4.7 Regression Model Line



ROC Curve

To assist with better defining exercise EFL for future work, a ROC curve test was performed. We sought to determine what percentage of overlapping between the baseline flow volume loop and exercise flow volume loop would give a positive detection of exercise expiratory flow limitation. Results of the ROC curve are shown in Figure 4.8.

The ROC curve test demonstrated the area under the curve to be 93.9% with asymptotic significance =0.001). If the percentage of overlap between exercise flow volume loop and baseline flow volume loop was greater than or equal to 0.7375 (73.75% overlap), there was an 83.3% chance the test would correctly identify the individual as having exercise expiratory flow limitation and 4.5% chance that a person without exercise expiratory flow limitation would be incorrectly identified with flow limitation (Table 4.7).

Figure 4.8 ROC Curve of percent overlap between the exercise flow volume loops and baseline flow volume loop

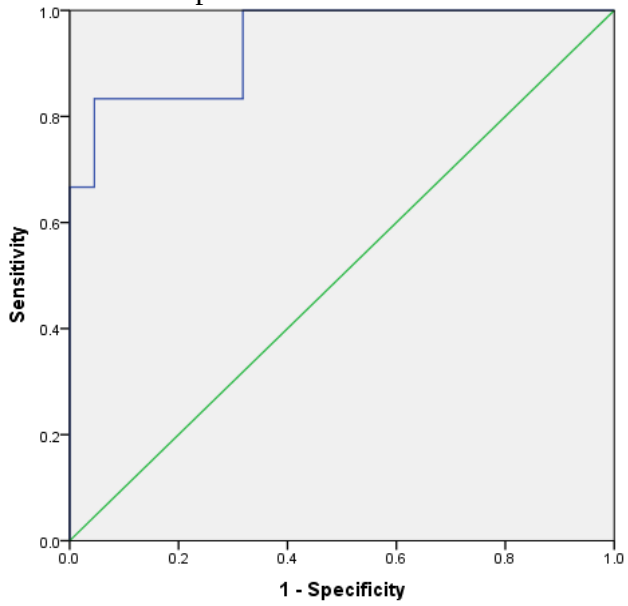


Table 4.7 Coordinates of the curve

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
.0000	1.000	1.000
.2695	1.000	.955
.4075	1.000	.909
.4400	1.000	.864
.4605	1.000	.818
.4705	1.000	.773
.4730	1.000	.727
.4945	1.000	.682
.5155	1.000	.636
.5405	1.000	.591
.5750	1.000	.545
.5940	1.000	.500
.6075	1.000	.455
.6155	1.000	.409
.6215	1.000	.364
.6440	1.000	.318
.6725	.833	.318
.6880	.833	.273
.7045	.833	.227
.7185	.833	.182
.7285	.833	.136
.7375	.833	.045
.7405	.667	.045
.7435	.667	.000
.7670	.500	.000
.7975	.333	.000
.8630	.167	.000
1.0000	.000	.000

Tracheal Diameters

Tracheal diameter was measured by ultrasound in eight participants to determine the feasibility of this measurement. The average tracheal diameter was 10.1 ± 12.0mm (EFL (combined DEFL and BEFL) n=2, tracheal diameter= 9.25 ± 0.05mm; NEFL n=6, tracheal diameter =10.5 ± 0.120mm). To investigate dysanapsis, the ratio of tracheal diameter to FVC was calculated and found to be not significantly different between groups (EFL=0.202 ± 0.003mm·L; NEFL = 0.252 ± 0.055mm·L, p= 0.265). The cricoid cartiledge arch was visible in all eight participants tested. Average tracheal diameter measurement for each participant can be found in table 4.6.

Table 4.8 Individual tracheal diameters and tracheal diameter to forced vital capacity ratio

Inner Cricoid Cartilage Tracheal Diameter (mm)	Outer Cricoid Cartilage Tracheal Diameter (mm)	TD:FVC (mm·L)
9.32 ± 0.069	15.33 ±0.06	0.255 ± 0.019
9.62 ± 0.051	15.22 ± 0.04	0.182 ± 0.010
12.00 ± 0.066	16.83 ± 0.03	0.248 ± 0.013
11.33 ± 0.055	16.93 ± 0.02	0.215 ± 0.010
9.33 ± 0.067	14.22 ± 0.10	0.345 ± 0.025
9.73 ± 0.093	14.96 ± 0.06	0.228 ± 0.020
11.37 ± 0.047	16.46 ± 0.11	0.302 ± 0.011
9.71 ± 0.035	15.35 ± 0.07	0.199 ± 0.007

Average of the 3 measurements per participant ± the standard deviation between measurements.
TD: tracheal diameter, FVC: forced vital capacity

DISCUSSION

The purpose of this study was to describe the differences in ventilatory mechanics during exercise and exercise capacity in female endurance athletes with and without exercise EFL. Our findings demonstrated three types of exercise expiratory flow limitation: the definite expiratory flow limitation (DEFL) with overlapping of the exercise flow volume loop with both pre- and post-exercise expiratory flow volume loop, the borderline expiratory flow limitation (BEFL) with overlapping of the exercise flow volume loop with only the pre-exercise expiratory flow volume loop, and the participants with no overlapping of the exercise flow volume loop (NEFL) with either the pre- or the post-exercise flow volume loops. We hypothesized that participants with EFL would have increased dynamic hyperinflation (DH) (demonstrated by increased EEV) and dyspnea with exercise. There was no significant difference in DH between groups, however the abdominal ribcage EEV had a significant constant load by group interaction. Despite spirometry being within the normal limits, pre-exercise FEV_1/FVC ratio, $FEF_{25-75\%}$ predicted and FEF_{25-75} (L) were significantly different between groups. After exercise the FEV_1/FVC ratio and $FEF_{25-75\%}$ predicted remained significantly different between groups. The increase in $FEF_{25-75\%}$ predicted from pre- to post-exercise spirometry was an independent predictor of %FVL reserve. Other independent predictors of %FVL reserve were the self report of excessive mucus production with exercise and increases in $PetCO_2$. Decreased $\%V_{RCp}$ was not an independent predictor but did contribute to the regression equation.

Expiratory Flow Limitation

Resting spirometry may prove to be insightful in identifying athletes that will achieve or surpass their voluntary forced expiration limits. Participants who exhibited overlapped flow volume curves with exercise had significantly lower FEV_1/FVC ratios, FEF_{25-75} (L) and FEF_{25-75}

% of normal predicted than NEFL participants. Despite being lower than NEFL, the FeV_1/FVC ratio and FEF_{25-75} were still within the normal range (FEV_1/FVC was 77%, predicted normal was 78%, FEF_{25-75} was 84% predicted). The NEFL group had supranormal FEV_1/FVC (84%, normal was 78%) and FEF_{25-75} (106% of predicted normal). Therefore, when exercise capacity is above average, such as in an endurance-trained athlete, in order to not have EFL, the large airways may need to be above average to accommodate the ventilatory demands of the athlete. Also, the increase in FEF_{25-75}% predicted from pre to post exercise was an independent predictor of %FVL reserve. The connection between increased bronchodilation with exercise and flow limitation gives us the impression that perhaps the participants in the DEFL group and BEFL group may have a degree of very subtle asthma or inflammation at rest that can be overcome in some participants with exercise. Therefore, when screening for EFL, participants with lower FEF_{25-75} may be more likely to demonstrate EFL. This finding is supported by that of Dominilli et al., who found participants with EFL to have a significantly greater drop from FEF_{75} to FEF_{50} and FEF_{50} to FEF_{25} ($L \cdot min^{-1}$) (63), supporting our findings that FEF_{25-75} is decreased in participants with EFL. Future work may want to consider the FEF_{25-75} measurement when analyzing or determining EFL in female endurance athletes.

Ventilatory Limitation

The increase in $PetCO_2$ with exercise in participants with DEFL and BEFL was not surprising based on the findings of previous literature (32). Work on cyclists has found $PetCO_2$ to drop near maximal exercise due to the hyperventilatory response driven by acidosis (105). However, due to inadequate hyperventilation potentially from respiratory muscle fatigue (32) participants with EFL begin to retain carbon dioxide at high intensity exercise. In one study by

Bussotti et al., increased $PetCO_2$ in cyclists corresponded with greater tidal volumes, lower respiratory rate and higher peak aerobic capacity (106).

Increased $PetCO_2$ has also been associated with DH. About one-third of the participants in this study demonstrated DH at maximal exercise but not during either of the submaximal exercise tests; these findings were similarly observed in women with EFL and with NEFL. For all participants who exhibited DH, similar levels of dyspnea were observed with higher muscle fatigue scores. Evidence of DH has often been attributed to flow limitation, and it is accompanied by increased dyspnea (more than muscle fatigue) and hypercapnia in patients with COPD (5, 34, 73, 107). However, COPD patients also have ventilation perfusion mismatch, damaged pulmonary capillary beds, increased inflammation and decreased elastic recoil that can influence dyspnea beside DH (108). In addition, similar to our results, other work has found DH has been observed in the absence of flow limitation in athletes (7, 8, 32, 46).

Supporting the previous findings in female endurance athletes (34, 109), participants in this study, many whom achieved their MVV, demonstrated on average <10% breathing reserve at peak exercise. However, the lack of breathing reserve in participants in this study was not associated with greater dyspnea but instead higher RPE and can be explained by work performed by Dempsey et al. and Harms et al. Dempsey et al. demonstrated a central feedback mechanism that caused increased sensory stimulation in the periphery when diaphragm fatigue increased (110). Harms et al. demonstrated a shunting of blood flow from the periphery to the respiratory muscles at maximal exercise leading to decreased oxidative capacity in the peripheral skeletal muscle (78, 110). It is possible that the decrease in breathing reserve did not elicit greater dyspnea compared to overall perceived exertion because sensation and fatigue in the periphery are increased with increased ventilatory fatigue and work. Also, the measurement of dyspnea and

perceived exertion are subjective and therefore left to participant's interpretation of the question, allowing for variation between the physiological objective responses and these subjective measurements.

Ventilatory Mechanics

The optoelectronic plethysmography of our participants' chest walls revealed that from the 60% constant-load test to the 85% constant-load test, the participants with no exercise EFL (NEFL) significantly decreased their pulmonary ribcage percent contribution to total tidal volume ($\%V_{RCp}$) and significantly increased their abdomen percent contribution ($\%V_{Ab}$). This pattern demonstrates what has been defined as normal breathing mechanics in previous work where the abdomen muscles are recruited with higher intensity and deeper tidal volumes (141). Whereas participants with exercise EFL did not have such a dramatic switch from pulmonary ribcage recruitment to abdomen, but rather decreased $\%V_{Ab}$ with increased intensity and significantly increased abdominal ribcage compartment contribution ($\%V_{RCa}$) compared to the group with NEFL. The abdominal ribcage area has been found to correspond with the movement of the diaphragm (18, 111). In previous work on EFL, flow limitation was associated with increased resistive work (64, 107). Increased resistant work has been associated with increased diaphragm recruitment (5, 112). Therefore, the increased volume change from the abdominal ribcage area in participants with DEFL and BEFL could potentially be representative of increased diaphragm recruitment. Also, the abdominal muscles have been shown to demonstrate fatigue at work >90% maximal aerobic capacity (141, 142). It is possible that due to the increased resistive work of breathing from exercise EFL, the abdominal muscles of the group with EFL were demonstrating fatigue early than those with NEFL; however this hypothesis would need further research.

Another alteration in breathing mechanics was observed when comparing the abdominal ribcage EEV during the 60% constant-load test to the abdominal ribcage EEV during the 85% constant-load test. Participants with exercise EFL had a greater decrease in EEV with higher intensity that the participants with NEFL. This finding was unexpected, however it corresponds with that of Mota et al., who found that male cyclists (with no exercise EFL) decreased EEV during moderate levels of exercise but increased EEV at higher intensities due to the hyperventilatory response often observed at maximum exercise (46). A potential reason why the participants with exercise EFL did not increase abdominal ribcage EEV may be because EFL has been found to impede this natural hyperventilatory response at maximal exercise.

EIA- Like Symptoms and EFL

In some studies, EIA-like symptoms have been reported to be more common in female athletes compared with male athletes, leading some to propose that the increased turbulent flow associated with EIA causes inflammation (68, 70). Because flow resistance increases with EFL, we hypothesized that participants with EFL would have increased EIA-like symptoms. In our population, mucus production was predictive of EFL.

Anderson et al. found that increased injury to the airway epithelium causes increased inflammation and mucus production (70). Anderson attributes the narrowing of the airways to be due to inflammation. The nature of this relationship makes it difficult to differentiate if the EFL causes the inflammation or the inflammation causes the EFL. The asthma-like symptoms of elite athletes have been attributed to an asthma caused by chronic stress and inflammation altering the smooth muscle, as opposed to classic asthma found in non-athletes (16). Ali et al. has suggested

that physicians treat athletes with these non-classic, asthma-like symptoms with anti-inflammatory drugs before beta-agonists (113).

Limitations

OEP has been used to measure end-expiratory volumes and thus DH in a selection of studies and populations (17, 50, 114, 115). However, this technique has not been validated against the negative expiratory pressure technique used to measure DH in previous work (29) or the increase in inspiratory capacity technique (62). A benefit to OEP is that natural breathing does not have to be altered to measure EEV; altered ventilatory pattern has been stated as a limitation of the other techniques (29). Also, performing the correct maneuvers during exercise is difficult and can give false decreases in inspiratory capacity, thus leading one to believe that EEV increased when it did not (116). This ability to capture natural breathing pattern and use non-invasive measures made OEP preferred over other possible measurement forms. However, until it is validated against previous measurements, it is difficult to know if variations between results are due to measurement variability. A second limitation of the study is the subjective nature of dyspnea and muscle fatigue measurements. Despite the modified Borg scale being a commonly used tool for measuring level of dyspnea and perceived exertion, this subjective measurement can have limitations. Mastroianni et al. found that participants underestimated their level of heart rate by perceived exertion when carrying various loads while hiking (117). Thompson et al. describe the difficulty of setting exercise intensity from RPE. The RPE reported at a given lactate and heart-rate level during a graded exercise test did not correspond to the RPE reported when at the same intensity in the field (118). To the contrary, Noble et al. found a very good correlation with RPE and physiological measurements such as lactate and heart rate (119). Also, although perceived dyspnea and exertion are subjective measures they have been

recognized as markers of homeostatic disturbance, therefore making the measurement useful despite its limitations (120).

Future Work

To identify a potential percent overlap between the exercise flow volume loop and the baseline flow volume loop we performed an ROC curve. We observed that an overlap of 73.75% or greater may be a potentially used to positively identify EFL. Future work is needed to determine the diagnostic value of this reference point in helping to determine the potential cause for symptoms or physiological changes that often correspond with exercise EFL.

Also, the variation in breathing mechanics in the EFL group could potentially be present in mild COPD patients. Future work could investigate if female patients' with mild forms of COPD demonstrate similar ventilatory mechanics with exercise to female athletes with EFL. Future work could also take this study a step further and after identifying endurance athletes with EFL, collect airway inflammatory markers before and after field tests in various environments to determine if the athletes with EFL have increased airway inflammation and what role seasonal factors play in this population.

Conclusion

In conclusion, this study gives further insight into the impact of EFL on female athletes' ventilatory mechanics and exercise capacity. We found that flow limitation was not associated with decreased functional capacity when compared to similarly trained participants with NEFL. A potential reason for these participants maintaining functional capacity may be due to a compensatory response in ventilatory mechanics; however, future work is needed to further investigate this theory. We also concluded that baseline FEV_1/FVC and FEF_{25-75} % predicted

were commonly lower in participants with EFL despite being in the normal range. By investigating the %FVL reserve we were able to analyze the concept of flow limitation as a continuum and found the $PetCO_2$, increased FEF_{25-75} % predicted with exercise and self-report of excessive mucus production with exercise were all independent predictors of a decreased flow volume loop reserve and a potential limitation of the airways to accommodate the ventilatory demands of high-intensity exercise in these athletes.

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APPENDIX A

Literature Review

Introduction

During exercise, regulation of oxygen, carbon dioxide and pH all begin and end with alveolar ventilation. Exchange of air between the atmosphere and the alveoli can be influenced by the mechanical properties and interactions between the lung, chest wall and muscles (55). The interaction between lung volume, flow and muscle activation comprise our mechanics(123). Impaired or inefficient ventilatory mechanics has been associated with excessive shortness of breath and impaired exercise tolerance (25). Impaired ventilatory mechanics has been described as increased work and movement of the diaphragm or abdominal compartment that does not result in increased flow. The lungs have been widely considered to be "over built" for metabolic demands of the body, but well-trained endurance athletes may achieve their maximal ventilation and therefore be limited by the ventilatory system (25). Accumulating evidence has demonstrated that exercise tolerance may be attenuated by exercising close or at maximal ventilation, however the findings are not definitive. By further investigating the role of the ventilatory system and how it is impacted by high volumes of endurance exercise, it may be possible to decipher if there are adaptations or limitations to the ventilatory system to exercise in such athletes.

The purpose of this comprehensive literature review will be to discuss the following: exercise respiratory physiology and respiratory responses to exercise, exercise ventilatory mechanics, differences in the mechanical properties of the ventilatory systems between women and men, and the potential ventilatory limitations to exercise. The goal of this review is to

determine if there are differences between endurance athletes' and non athletes' respiratory mechanics and physiology. Additional questions to be addressed include, "How does exercise impact on ventilatory mechanics?", "How do the ventilatory systems of women differ from men?", Do these differences impact exercise capacity or performance?", and to determine if there is need for further research in any of the potential aspects of ventilatory limitations to exercise.

Historical Background

The measurement of gas exchange and the pressure of oxygen and carbon dioxide is contributed to work performed in the 1920's by Noyons, Hill and Ledig & Lyman who designed the first gas analyzers as sited in Berg et al. (124). But it was after World War II that the knowledge of pulmonary gas exchange truly expanded. Fenn et al.. first diagramed gas exchanged and related the six variables, partial pressure of oxygen, partial pressure of carbon dioxide, the respiratory exchange ratio, arterial oxygen saturation, alveolar ventilation and the effects of altitude in 1946. It was Fenn's work along with Richard Riley at the US Naval School and Aviation Medicine, who developed the ability to measure the partial pressure of oxygen and carbon dioxide in the blood stream and lead science to the current understanding of ventilation-perfusion (125-127). From the work of Fenn and Riley science now understood that breathing was a combination of passive perfusion across a gradient and active ventilation dictated by the surrounding musculature.

Respiratory Physiology and Responses to Exercise

An essential organ for exercise, the lungs provide a barrier between the ambient air and the body's internal fluid environment allowing for the vital metabolic reagent, oxygen, to enter the blood stream and a metabolic byproduct, carbon dioxide, to be expelled. This diffusion of gases across the alveolar membrane into the blood stream is governed by Fick's Law, which states that the rate of diffusion is directly proportional to the surface area, diffusion constant and pressure differential of the gases. Fick's law governs gas diffusion through the alveoli into the blood stream. In combination with gas diffusion, ventilation needs to occur in order to circulate carbon dioxide out of the lungs and oxygen into the lungs.

Ventilation is an active process driven by the neural-respiratory unit of the brain and carried out by the musculature of the thoracic cavity and abdominals (96). During exercise, increased muscular metabolic demand drives greater extraction of oxygen from the blood and increases metabolic byproduct. Work performed by Asmussen et al. in 1943 theorized that reflexes in the working muscle triggered responses from a higher command center or the respiration center of the brain stem (128). This theory was supported by early work in animal non-human models that demonstrated an area in the brain stem that was stimulated during respiration (129-131). Asmussen continued to develop evidence of the relationship between muscular contraction, lactic acid production and oxygen debt on ventilatory responses (132). He connected the presence of blood pyruvate and respiratory drive during heavy exercise (133). Work by Gray et al. demonstrated that increases in ventilation were multifactorial and H+, pCO2 and pO2 all exerted independent effects on ventilation. Grey described how it was the sum of these effects that was demonstrated by the final ventilatory response (129, 134). Work by Euler et al. supported the influence of CO_2 levels in the blood stream on respiratory response by highlighting the response in the medulla to increased circulating CO_2 in the cat (129, 135). The

combination of these works explains the relationship between the change of blood acid-base balance and respiration center. Alterations in blood pH were found to be detected by the peripheral chemoreceptors that then signal the dorsal respiratory group in the respiration center and excite the respiratory muscles to increase ventilation (136). During exercise the ventral respiratory group was found to be also activated allowing for even greater signaling of the inspiratory and expiratory neurons causing increased ventilatory effort and better clearance of carbon dioxide (CO_2) and H^+ to prevent blood acidosis (136). Therefore increased blood acidosis indirectly drives increased activation of the ventilatory muscles.

Resting ventilation has been found to be mostly a passive process dictated by the pressure differentials within the chest and activation of the diaphragm and intercostals (137). During activity, ventilation was found to become an active process of increased activity by the diaphragm and abdominals, driven by the level of CO_2 and H^+ in the blood. The increased activity of the ventilatory muscles creates a greater pressure differential leading to increased tidal volumes (Vt) (138). Greater Vt leads to increase minute ventilation (Ve) until above the ventilatory threshold. Once exercise intensity exceeded the ventilatory threshold, Vt was found to plateau and respiratory rate became the driving force in increased Ve (34).

The demands of the ventilatory system are even greater in endurance athletes due to their increased aerobic capacity. Endurance athletes were found to have increased elastic work and blood flow demand by the respiratory muscles because of the ability for these individuals to exercise for extended periods of time above the ventilatory threshold (24, 34, 138). During activity greater than ~85% of maximal aerobic capacity (VO_2 max), respiratory muscles (specifically the diaphragm) were found to demonstrate fatigue (139-141) and exercise >90% VO_2 max elicited abdominal fatigue (141, 142). There has been no evidence that human lung

parenchyma or airways adapt to physical training or respiratory muscles hypertrophy from endurance training or become decondition from bed rest (23), but in 1978 Keens et al. found that rat ventilatory muscles hypertrophied from inspiratory loading and theorized that human muscle may do the same (143, 144). In 1990, Powers et al. found that after 45 days of 5 times per week of endurance training rats' costal diaphragm and intercostals muscles improved oxidative capacity. Work by Hsia in 2000 demonstrated that in dogs ventilatory muscles did not hypertrophy after 8 weeks of endurance activity but oxidative capacity increased primarily due to increased blood flow and neural activity (145). During high intensity aerobic exercise in endurance athletes, 16% of the total maximal aerobic capacity (VO2 max) was contributed to the respiratory muscles (141, 146). Work by Wilhite et al. found that improvements in oxygen update during altitude training actually fueled the respiratory muscles rather than the peripheral due to increased blood flow, capillary density and oxygen carrying capacity of the respiratory muscles (147). The impact of this increased demand of the pulmonary system and how it impacts exercise tolerance will be discussed further in "Ventilatory Limitations to Exercise" below.

Exercise Ventilatory Mechanics

The respiratory muscles have been found to be anatomically suited to meet the needs of exercise ventilatory demand with minimal work and neural regulation optimized (141). Polla et al. described the muscle groups activated during inspiration to be the "diaphragm, scalenus, sternomastoid, parasternal, internal intercostal, and external intercostal muscles" while the muscles activated during expiration were the "internal intercostal and abdominal muscles" (148). The average fiber type make up of the diaphragm was found to be 55% slow twitch, 21% fast oxidative and 24% fast glycolytic, with high capillary density and short diffusion distance allowing for high oxidative capacity and fatigue resistance. In comparison, the abdominals were

found to be approximately 50% type I muscle fiber and 50% type II and the intercostals had a slightly higher percentage of type I muscle fibers with 60% type I muscle fibers, and 40% type II (148, 149). This distribution of fiber types makes the respiratory system built for endurance and explosive capacity (149). Studies have demonstrated that the diaphragm has specialized isoforms (RyR3) that have increased excitation to stimulants when compared to other muscle groups in the body (148, 150, 151). It is not known to why the diaphragm would have this specialized isoform but authors theorized that it may allow for even faster and greater reaction to stimulants (148). Research has also found that the diaphragm appears to be the crucial muscle in ventilation and when compromised (such as in severe COPD with lung hyperinflation) can severely impact breathing mechanics (5). Disease and intense exercise are known to cause increased work of breathing which then impacts breathing mechanics (28, 152).

Classic work by Rohrer described how resistance within the ventilatory system impacts breathing mechanics (109) and is considered the original theories on breathing mechanics (138). Rohrer describe resistive and elastic forces that the ventilatory muscles must overcome to inhale and exhale (138). In Rohrer's work, the elastic work was the force of overcoming the stretch of the lung tissue from resting volume to peak tidal volume and was calculated by the pressure x the volume displacement from rest (138, 153, 154). The second force Rhorer described was the resistive work that the ventilatory muscles must overcome caused by air viscous and turbulent forces (109, 155). Rohrer's calculation demonstrated that resistive work increased with greater tidal volume (109, 155). This work was continued by Briscoe et al. in 1958, who described the relationship between the airways radius and length and the lung conductance of air to the alveoli. Briscoe described that the resistance in children to be 3-5x that of an adult due to their still developing airways (155). The resistive work of breathing was also found to be higher in women

than men because men develop an "Adam's Apple" or larger larynx that widens their trachea helping to accommodate the large tidal volumes generated during exercise (60). Therefore the work of breathing has been determined to be the energy needed to overcome both the elastic work and resistive work to increase Ve and meet the demands of the exercise.

Measurement of Ventilatory Mechanics

The classic work by Fenn, Rahn and Otis utilized mathematical equations to analyze breathing mechanics and resistive and elastic forces (138, 156). These equations were the fundamental basis for modern day testing. But by 1960 breathing mechanics could be measured invasively and directly. The development of esophageal and gastric balloons combined with electromyography (EMG) allowed scientist to capture and analyze intrathoracic pressures and movement of the respiratory muscles. Agostoni and Rahn demonstrated that the contribution of the thoracic and abdominal compartments during ventilation could be detected by a combination of pressure measurements and lung volume measurements during static and dynamic ventilatory maneuvers (137, 157). However this form of testing mechanics had its limitations. The pressures could not be obtained during exercise and were an uncomfortable invasive procedure that gave little information on volume changes within the chest wall (8). Also in order to measure fatigue, a combination of pressure measurement and nerve stimulation was often used and gave high levels of error if certain conditions are not monitored closely (141). Romer et al. described the factors of potential sources of error to be; supramaximal stimulation (158), isovolumic conditions (159), abdominal compliance (160), and postactiviation potential (161) (141). Thus researchers' continued to experiment with alternative forms of measuring ventilatory mechanics.

In 1967 Konno and Mead devised a way noninvasive way to measure volume displacement within the chest wall (8). Konno and Mead divided the chest wall into 2 parts, the ribcage and the abdomen with the coastal line being the margin between compartments. Their techniques were based on the relationship between volume and linear motion. Their technique involved linear transducers to be connected to threads surrounding the individual's body surface and a pulley that connected the threads to the ribcage and abdomen. Signals from the transducer were recorded with the ribcage's movement displacement on the Y and the abdomen on the X axis. A spirometer was placed in the subject's mouth to measure pulmonary function. Konno and Mead discovered that the contribution to tidal volume from the abdomen was higher in the supine position than upright and when one compartment was restricted the other compartment would increase volume displacement. The limitation of this method was that the diaphragm was not isolated and therefore it's contribution to Vt neglected (162). Other methodology was also devised to attempt to measure breathing mechanics in a noninvasive manner but that too had its limitations. In 1977 Guenard et al. reported using integrated flow plethysmography to measure the mechanical characteristics of the ventilatory muscles during exercise (163). However analyzing breathing in a plethysmography box posed some issues that made it not ideal for exercise breathing mechanics such as; subjects still have to perform breathing maneuvers during exercise to acquire lung volumes and mechanics therefore natural breathing patterns could not be acquired, temperature and humidity regulation in the box was difficult due to the need to keep the box sealed to measure volume, muscle mechanics were not measured only airway and calibration of the system problematic (164, 165). A technique that was based off the work of Konno and Mead used a X-ray computed tomography to construct a three dimensional imaging of the chest wall and measure the volume changes (166). This technique allowed the researchers

to partition the ribcage into the pulmonary ribcage and the diaphragm. Although this technique was extremely accurate it exposed the individual to high amount of radiation and values could only be obtained in the supine position (166). Thus until 1990 and the invention of motion analysis, knowledge of unaltered exercise breathing mechanics was limited.

The first motion analysis system used for analyzing breathing mechanics was a combination of the ELITE system (a television processor system) and the OR (an optical reflectance motion analysis system) (11). This system was originally devised for limb motion analysis but in 1994 Ferrigno et al. utilized an algorithm to calculate 3 dimensional chest wall volume changes using the ELITE plus OR system that could be used at rest and during exercise (167). The first system utilized 4 cameras and 32 markers to acquire volume changes. Although this system correlated strongly with spirometry the percent error was high (21.3% BTPS) (10). Therefore in 1996 Cala et al. utilized the technology designed by Ferrigno but extended the boundaries of the chest wall to better outline the costal margin and used 86 rather than 32 markers for increased accuracy (10). Cala's improvements decreased the error substantially to ~2% for tidal volume and <3.5% for change in tidal volume. An error prediction equation calculated that in any given cross sectional area across the entire chest wall, % error was about 7-8% (10). In 1997 , the first study utilized motion analysis software to analyze chest wall mechanics during exercise (6). Kenyon et al. described the ribcage mechanics of 5 men (age 31-38) performing an incremental exercise test to exhaustion (6). Aliverti et al. expanded upon these findings to describe the relationship between the diaphragm area (the abdominal ribcage) and the abdomen (18). The ELITE system evolved into what is now known as Optoelectronic Plethysmography (OEP) in 2000 (3). OEP was utilized to measure asynchrony between chest wall compartments and increased end-expiratory volume in chronic obstructive pulmonary

disease COPD (16). Vogiatis et al. was the first to compare the breathing mechanics of men and women during exercise (10 men, 5 women). A flaw of this study was the lack of isolation of the diaphragm area (50), thus over looking gender differences in breathing mechanics that were detected in later work (81). Currently, OEP has been utilized to analyze chest wall mechanics in an array of populations such as lung transplant patients (51, 168), patients with pectus excavatum (169), heart failure patients (170), neuromuscular disease patients (171, 172) and healthy athletes (81).

Differences between Male and Female Ventilatory Systems

Anatomical variations have been found to cause increased elastic work as described previously. These variations alter pulmonary dynamics, increase sheer stress and inflammation and possibly limit responses to exercise (25, 28, 60, 68). Anatomical variations between women and men span from the trachea through the alveolar bed. Women have up to 40% smaller trachea to lung volume ratios, corrected for lung and body size, than do men (38, 60-62). In a study performed by Brooks et al., there was a positive correlation between tracheal cross sectional area and vital capacity in males and not in females (61). Brook's findings supported those of Mead et al. in that dysanapsis was more likely to occur in women, and the growth of parenchyma and tracheal diameters are independent of one another (60, 61). A smaller tracheal to parenchyma ratio may become an issue when the demands on the ventilatory system are very high, such as during heavy exercise. During high intensity exercise, expiratory flow resistance can increase as much as four times more than resting levels (138). In elite endurance woman athletes, the resistance through the trachea from dysanapsis may cause sheer stress and be the cause of flow

limitations during exercise, vocal cord dysfunction (67), inflammation (68), and possible dynamic hyperinflation (28, 63).

Beyond the airways, differences in the chest wall in women and men may cause altered ventilation mechanics. Within the chest wall, women have been found to have a greater ribcage angle allowing for increased movement through the pulmonary ribcage during ventilation (37, 81, 173). The difference between men and women's ribcages were found to cause decreased tonic abdominal muscle activity, smaller radial ribcage dimensions and higher diaphragm height (56, 174). Bellemare et al. found that the smaller lung volumes produced by women were caused by smaller radial ribcage (174). The variation in ribcage mechanics and dimensions may be the cause of altered ventilatory mechanics described by Layton et al. and Romie et al. (37, 81). Romie et al. found that, women had greater volume displacement in the pulmonary ribcage compartment than in the abdominal ribcage (where the diaphragm inserts) and abdominals during sitting and supine rest (37). This was unlike men who were found to have equal volume displacement in the pulmonary ribcage and abdomen (37). These findings were confirmed during exercise by Layton et al. who found women of varying fitness levels to have greater volume displacement in the pulmonary ribcage than in the abdominals at rest and throughout exercise (81). The influence of ribcage mechanics went beyond volume distribution. Ribcage displacement has been found to impact diaphragmatic mechanics. Women with smaller ribcages were associated with shorter diaphragm length. The shorter diaphragm length preserved diaphragm mechanics and shortening velocity (56). During exercise, women were found to have decreased diaphragmatic fatigue (82). It is possible that because of the ribcage dimensions preserve diaphragm length, the diaphragm has a mechanical advantage that allows for better work efficiency during exercise. However women have been found to demonstrate increased

work of breathing during exercise when compared to men (28, 75). Sheel et al. described the increased work of breathing in women as complex and multifaceted (55).

Sheel's work described the elastic work of breathing needed to overcome anatomical structure changes and the resistive work needed to overcome flow resistance (55). As exercise intensity increases, the work of breathing becomes disproportionate between women and men. Because women have smaller lungs for a given body size (34) they utilize a greater amount of their ventilatory reserve and have an increased work to breath (28, 34). At minute ventilations (Ve) greater than 90 $L \bullet min^{-1}$, women were found to have twice the work of breathing than their male counterparts (28, 55). Although women's smaller lungs was believed to contribute to this increased work to breathe, Sheel et al. suggested that a larger contribution may be presented by the work to ventilate against the turbulent airflow created by the narrower tracheas and bronchi (55).

Ventilatory Limitations to Exercise

Researchers such as JA Dempsey, DC McKenzie and HC Haverkamp have demonstrated that the adaptations to endurance exercise can exceed the limitations of the ventilatory system (175). West et al. has hypothesized that sheer stress to the airways can cause breaks in the pulmonary capillary membrane that interferes with gas exchange (176). Therefore components of the ventilatory system that have been linked to limited exercise tolerance have been; ventilatory muscle fatigue, limitations of the airways, insufficient arterial oxygen exchange (25).

Neurological Feedback Mechanisms

Neurological feedback mechanisms associated with ventilatory fatigue have been demonstrated to impact peripheral musculature blood flow and thus limiting the continuation of exercise. Researchers have found that at maximal exercise capacity, increased energy expenditure from ventilatory muscle work caused a redistribution of blood flow away from the working skeletal muscle to the abdominal, diaphragm and intercostal musculature (24, 177). This redistribution of blood flow to the ventilatory muscles contributed to decreased skeletal muscle aerobic capacity in endurance athletes (24). Secondly, a neurological feedback system has been established between diaphragm fatigue and alteration in peripheral stimulation. In 2000 Hill et al. found that in the rat, diaphragm fatigue elicited an increase in sensory fibers in the peripheral muscle that stimulated a reflexive response in the muscle to have prolonged relaxation phases during contraction thus potentially decreasing intensity and allowing for more recovery time between muscle contractions (Hill 2000). In 2002, Dempsey et al. described a similar relationship in the humans (114). Neurological feedback from the diaphragm signaled the central nervous system (CNS) to stimulate vasoconstriction peripherally, leading to increased peripheral fatigue and decreasing oxygen transport to the skeletal muscles (114). A study by Fregosi and Dempsey had also found that circulating blood lactate triggered a glycogen sparing effect in the respiratory muscles (178). Fregosi also found that when comparing time to diaphragm fatigue by electrical stimulation, when circulating lactate levels were present diaphragmatic fatigue occurred at an earlier level. This result lead Fregosi to link the potential relationship between high blood lactate levels increase diaphragm fatigue (178). Based on the findings of these studies (114, 178), Babcock et al. performed several studies to investigate the effects of diaphragm fatigue on exercise capacity and vice versa. Babcock described how the diaphragm fatigues much earlier to stimulation in the presence of whole body exercise than when the diaphragm was

stimulated in the presence of no exercise. Babcock et al. also found that diaphragm fatigue limited the hyperventilatory response at maximal exercise, but did not report a decrease in performance (179).

The findings of how diaphragm fatigue impacts performance have unfortunately been inconclusive, and very few studies have used nerve stimulation to measure the effects of respiratory muscle fatigue on exercise tolerance but rather use more subjective measurements such as perceived exertion (141). Consequently, further research is needed to determine how diaphragm fatigue impacts performance. Sound evidence is needed to establish if the neurological feedback system that acts as a protective mechanism between the ventilatory system and skeletal musculature in fact inhibits an individual from continuing exercise in the presence of ventilatory fatigue.

Airway Limitations

Exercised Induced Asthma (EIA):

In persons with known asthma, EIA has been found to be very common (prevalence of ~75%) (70). However in recent years, studies have found the increased prevalence of EIA in healthy non-asthmatics to be on the rise. From 1984 to 1996 the percentage of athletes with EIA increased from 11.2% to 16.2% (70, 180). One potential reason that researchers have proposed is that exercise itself causes increased bronchial hyper-responsiveness (BHR) (70). Heavy breathing was found to cause the nose to be bypassed, allowing cool, dry air to enter the airways and cause dehydration of the airway surface liquid. Research has found that the small airways are recruited during exercise to help humidify the air before it enters the lungs (68). During this process, the mucosal membrane of the airways dries, leaving the airways vulnerable to injury

(68, 70). The dehydration in airway surface area causes a decreased volume of the epithelial cells in the airways (68, 181, 182). The loss of volume in the epithelial cells created a change in their biochemistry causing them to constrict when previously they had dilated(70). An increase in inflammatory markers was also observed within the airways, and this is believed to cause airway narrowing (70, 183). The cause of the inflammation was theorized to be due to sheer stress within the airways (184). Inflammation has been found in the airways of runners, swimmers, skiers, and ice hockey players among other athletes (185-189).

Depending on the season that the athlete competes in, the test that will identify inflammation or BHR may vary. Holzer et al. found that summer endurance athletes were less likely to respond to methacholine provocation tests than eucapnic voluntary hyperventilation tests (EVH) or dry manntiol (68, 190). Whereas winter athletes were found to be the opposite, cross country skiers were found to respond to methacholine testing but not EVH or exercise provocation (191). Anderson et al. believed that the reason for the variations between seasonal athletes to provocation tests may be because the summer group had more exposure to airbourne pathogens and atopy that irritate the airways and cause increased immune response. This is different from the inflammatory response created by cold dry air in winter athletes (68). Work by Hemmingson et al. supported that the cold air was the stimulus for BHR in winter athletes by a return of normal airway response in the off season (192). In one of the few studies that longitudinally followed endurance athletes over the course of one year, found no changes in lung function from off season to competitive season (193). However this study took place in the Mediterranean, a region that has little fluctuation in air borne pathogens or temperature between seasons. It is possible that the 13 summer athletes tested did not demonstrate the seasonal changes in airway responsiveness observed in winter athletes because of the little variation in

climate. Therefore a similar study in either winter athletes and/or summer athletes in varying climates may be more insightful. The overall consensus of the research appears to be that exercise may cause increase BHR and lead to positive EIA testing. The underlying mechanism is most likely inflammatory due to drying of the airways or atopy depending on the athlete and season of competition.

Expiratory Flow Limitations:

Some studies have found that self reported symptoms of coughing, wheezing and excessive sputum production during exercise in athletes often does not correlate with a positive diagnosis of exercise induced asthma (EIA) (68, 187). Therefore alternative etiologies have been investigated to explain the prevalence of EIA-like symptoms in athletes. Up to 50% of endurance athletes have been found to report EIA symptoms, and these symptoms are especially prevalent in women (prevalence of symptoms is 35% to 13% women to men, respectively) (69, 187). Inflammation of the airways from either environmental stressors or sheer stress contributes to endurance athlete's symptoms (68, 187, 194). Green et al. believed that sheer stress caused by the ability to utilize large ventilation through a small trachea and bronchi could be a factor (195). The above phenomenon has been referred to as expiratory flow limitations and researchers attribute the increased sheer stress in the large airways to this (Verges 2005). Expiratory flow limitations can increase sheer stress during high intensity exercise because of increased airway resistance. Evidence demonstrates that resistance through the airways depends on radius, length, and volume of air through the airway (138, 155). Airway resistance has been found to increase by 4-fold when the lungs are completely inflated (155). Fry et al. tested the effects of impeded flow in patients with emphysema (196). Fry concluded that the impeded airflow from the emphysematous lung caused air to become trapped in the lungs, causing dynamic hyperinflation

of the lung (196). Many years later this concept was applied to another population with impeded flow: women. McClaran et al. found that during heavy exercise women were more prone to expiratory flow limitation than their male counterparts, leading to lower maximal expiratory flow rates (34, 55). Since these original works, multiple studies have confirmed the higher prevalence of flow limitations in women when compared to men (28, 75).

Despite the findings of flow limitations in women, female endurance athletes have not been well studied. Elite female athletes have been found to have is increased mechanical constraints to breathing (34), and thus may be more likely to experience ventilatory limitations to exercise. Elite endurance athletes need to a greater proportion of metabolic demand to the working muscle for peak performance; the excess energy costs of breathing needed to overcome flow limitations may be the difference between first and last place. Women with flow limitations were found to have twice the work to breathe than men without flow limitations when standardized for body size and work rate (28, 75). When comparing fit women to unfit women, Dominelli et al. found that smaller airways were the main contributor to flow limitation in the fit women (63). Johnson et al. found that flow limitations created a mechanical constraint to exercise hyperpnea in male endurance athletes, and the achievement of maximal ventilation corresponded with a plateau in oxygen consumption (29). Increased maximal expiratory flow resistance was also contributed to increased pressure within the pleural space, possibly leading to greater mechanical limitation (29). The increased pleural pressure caused by expiratory flow limitations may be representative of dynamic hyperinflation caused by air being trapped in the chest wall.

Dynamic Hyperinflation:

The presence of ventilatory flow limitations during exercise has been found to cause alterations in operational lung volumes (25, 62, 63, 91, 195). Dynamic hyperinflation in the chest wall occurs because flow limitation prolongs expiratory time, and thus the individual does not the full tidal volume before respiratory drive stimulates inhalation to occur. Therefore, air is trapped in the lungs and end-expiratory lung volumes increase rather than decrease (28, 91). Dynamic hyperinflation (DH) can create an increase in the work of breathing due to decreased elastic recoil and an increase in the work of the chest muscles to overcome the large lung volumes (60). This can become an issue for endurance athletes because during maximal exercise efforts blood flow to the working muscle is at high demand and any competition for blood flow could reduce aerobic capacity (24, 197). The implications of DH are a decrease in exercise tolerance and increase in dyspnea (76, 79).

Fit women are believed to be more likely to develop DH because of the presence of flow limitations and ability to achieve near maximal ventilations (28, 62). Dominelli 2011 et al. found, when comparing women of different fitness levels, more active women were more likely to have DH than less active women, and DH directly correlated to expiratory flow limitations (63). DH was calculated by comparing the inspiratory capacity maneuvers and mean expiratory flow rates during exercise. This technique has been the primary form of detecting DH during exercise (106, 198).

The impact of DH on exercise performance is still not well known. In a study by Cross et al., DH was found to cause an increase in slow component oxygen utilization (79). Cross believed that the increase in resistive work from DH caused an increase in energy demands by the subject and therefore contributing the slow component oxygen utilization (79). This was one of the few studies to investigate the impact of DH on oxygen kinetics in athletes. Dominelli et al.

also investigated the impact of DH on exercise and found that women who were more fit were more likely to have DH. The impact on exercise tolerance could not be determined (63). because the DH group and non DH group were not of equal fitness. Therefore, future research is needed to evaluate the impact of DH between women of equal fitness levels to determine if a person with DH would be a physiologic disadvantage and more work is needed in female endurance athletes to determine if DH occurs in a higher percentage of these women than what has been found in studies testing normal healthy women

Effects of EFL and DH Performance:

Iandelli et al. induced expiratory flow limitations in male athletes and found that the higher the expiratory flow pressure the greater the increase in dyspnea and greater impairment in exercise performance (76).

As discussed above, Cross et al. found that DH contributed to the increase in oxygen uptake slow component in exercise above the respiratory compensation threshold (79). A greater oxygen uptake slow component is thought to affect exercise performance (199, 200). Athletes with a greater oxygen uptake slow component will have a greater production of lactic acid and reliance on type II fibers (97, 201). A greater oxygen uptake slow component also may represent an earlier fatigue of type I fibers (79). This is all very pertinent to the endurance athlete. Knowing if an athlete has DH with exercise and at what intensity or duration of exercise it occurs could help coaches alter training regimens and racing strategies to maximize performance.

Also respiratory muscle fatigue has been thought to contribute to decrements in human performance under extreme conditions (29). Guenette et al. tested to determine if the higher cost

of breathing causes increased diaphragm fatigue and actually found the opposite effect. Women have greater fatigue resistance in the diaphragm after a maximal exercise test, compared with men (82). Therefore there may be an adaptation in ventilatory mechanics to DH that prevents diaphragm fatigue in women.

Lastly, Calverly et al. claimed that knowing if DH is occurring does not add to clinical relevance in care (202). However it is possible that based on Iandelli's findings, excessive dyspnea with exertion in a female athlete may be a strong indicator of flow limitation and DH. Therefore for clinicians treating a patient for increased dyspnea with exertion may want to take into consideration the possibility of flow limitations and DH with exercise. However further research is needed to determine if expiratory flow limitations and DH due in fact influence performance and are needed to be treated and if so what treatments that would be.

Insufficient Arterial Oxygen Exchange

Endurance athletes with large aerobic capacities will have a large capacity to extract oxygen from the blood stream and in return widen the alveolar –arterial pressure of oxygen difference ($P(A\text{-}a)O_2$) (25). Yet researchers have found that the alveolar membrane can only diffusion a certain amount of oxygen at a given time. When the $P(A\text{-}a)O_2$ difference widens to a certain point, the diffusion rate becomes limited and a perfusion/diffusion mismatch occurs, leading to arterial desaturation (25). Romer et al. measured arterial oxygen saturation in elite athletes and found that in some athletes oxygen saturation would decrease during high intensity exercise. The decease in oxygen saturation lead to increased quadriceps fatigue. When supplemental oxygen was supplied to the subjects, oxygen saturation remained at >98% and quadriceps fatigue decreased (203). Dempsey et al. found that exercise induced arterial hypoxemia (EIAH) caused increased pulmonary vascular pressures leading to increased potential

for pulmonary edema (204). High pulmonary vascular pressures can be contributed to increased cellular pressures from mechanical stress of breathing (205). Consequently these limitations usually only occur in very elite athletes during near maximal exercise. Harms et al. has also proposed a second possible explanation for arterial desaturation. Harms found that young women with large $P(A\text{-}a)O_2$ widening and insufficient hyperventilatory response were much more likely to experience EIAH than men (206). Conditioned women were more susceptible to EIAH than the less conditioned women, supporting the theory that athletes are more susceptible due to better oxygen extraction from the peripheral muscle. Billaut et al. investigated the impact of sex on the effects of arterial desaturation (SpO2) and neuromuscular fatigue. Results contradicted outcomes from Harms et al. (207). Billaut found no dimorphism between sexes with decreases in SpO2, but found that women demonstrated less peripheral musculature fatigue than men and thus less sensitivity to EIAH (207). Therefore findings are inconclusive as to whether EIAH is more common in women compared with men.

Dempsey et al. also described intrapulmonary shunting as a possible factor contributing to EIAH (25). Increased pulmonary artery pressure and an abnormally large $P(A\text{-}a)O_2$ have corresponded with increased intrapulmonary shunting in healthy subjects (208) and may be occurring in athletes demonstrating EIAH due to the large blood volume from the right side of the heart and widened $P(A\text{-}a)O_2$. Therefore widened P(A-a)O2 difference, limited membrane diffusion capacity, and large right heart blood volumes may all lead to EIAH in athletes.

Summary

In summary, research has supported the existence of ventilatory limitations to exercise in some endurance athletes. The potential causes may vary greatly from individual to individual. Women may be more susceptible than men to mechanical limitations and EIAH, while men

appear to be more susceptible to ventilatory muscle fatigue. Winter athletes are more likely to report EIA-like symptoms, but appear to be less sensitive to methacholine challenges than summer athletes, making diagnosis difficult. The mechanism for the cause of EIA symptoms is thought to be inflammation, but adequate treatment is still not defined. More research is needed to determine if EFL actually limits exercise performance in female endurance athletes or if potential compensatory mechanisms allow for continuation of exercise. There is also a lack of evidence implicating intrapulmonary shunting in athletes and the mechanism behind EIAH. Lastly, ventilatory muscle fatigue has corresponded to decreased peripheral blood flow and increased fatigue. Future work is needed to determine if some of the benefits of exercise in pulmonary disease patients (especially restrictive lung disease) may be the increased conditioning of ventilatory muscles.

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APPENDIX B

i. Definition of Abbreviations

EFL: Expiratory flow limitation

DH: Dynamic hyperinflation

OEP: Optoelectronic Plethysmography

BMI: Body Mass Index

Ve: minute ventilation.

V_t: tidal volumes.

PFT: pulmonary function test

MVV: Maximum voluntary ventilation.

FVC: Forced Vital Capacity.

FEV_1: Forced Vital Capacity in one second.

FEV_1/FVC: ratio of Forced Vital Capacity.

FEV_1: Forced Vital Capacity in one second over Forced Vital Capacity

FEF_{25-75}: peak expiratory flow at 25%, 50%, and 75% of the flow volume curve

f_B: breath frequency

ΔV_{RCp}: Change in volume within the pulmonary ribcage.

ΔV_{RCa}: Change in volume within the abdominal ribcage.

ΔV_{Ab}: Change in volume within the abdominal region.

$\%V_{RCp}$: contribution from the pulmonary ribcage to total change in volume.

$\%V_{RCa}$: contribution from the abdominal ribcage to total change in volume.

$\%V_{Ab}$: contribution from the abdominal region to total change in volume.

VCW,ei: chest wall absolute end-inspiratory volume.

RCp,ei: pulmonary ribcage absolute end-inspiratory volume.

RCa,ei: abdominal ribcage absolute end-inspiratory volume.

Ab, ei: abdominal absolute end-inspiratory volume.

CW,ee: chest wall absolute end-expiratory volume.

RCp,ee: pulmonary ribcage absolute end-expiratory volume.

RCa,ee: abdominal ribcage absolute end-expiratory volume.

Ab,ee: abdominal absolute end-expiratory volume

VT: ventilatory threshold

RCP: respiratory compensation point.

VO_2: oxygen uptake.

Ve/VCO_2: ventilatory equivalent for carbon dioxide.

Ve/VO2: the ventilatory equivalent for oxygen.

$PetCO_2$: end-tidal carbon dioxide pressure

Work: watts subject achieved at maximal exercise.

HR: heart rate.

RER: respiratory exchange ratio.

$V_D/V_{T:}$ Dead space ventilation

IC maneuver: Inspiratory capacity maneuver.

RPE: rate of perceived exertion

EFL: expiratory flow limitation

NEFL: no expiratory flow limitation

DEFL: definite flow expiratory limitation

BEFL: borderline flow expiratory limitation

DH: dynamic hyperinflation

EEV: end expiratory volume

COPD: chronic obstructive pulmonary disease

EIA: exercise induced asthma

%FVL reserve: the percent of baseline flow volume loop reserve at peak exercise as a representation of level of EFL.

TD: tracheal diameter

APPENDIX C

IRB approved consent and HIPPA form for Chapter III.

Columbia University Medical Center Consent Form

Attached to Protocol: IRB-AAAD5121
Principal Investigator: Matthew Bartels (mnb4)
IRB Protocol Title: Chest Wall Kinematics during Maximum Exercise test in Elite Cyclist.

Consent Number: **CF-AAAE1538**
Participation Duration: 1 day
Anticipated Number of Subjects: 40

Contact

Contact	Title	Contact Type	Numbers
Aimee Layton	Clinical Coordinator	Co-Investigator	Telephone: 212-305-0483 Cell: 201-602-9849
Renee Gerardo	Research Coordinator	Study Coordinator	Telephone: 212-305-9416

Research Purpose
The goal of this study is to test the differences in breathing between trained cyclists and untrained healthy people during a bike test. We will be able to measure how the lungs expand and contract during exercise using cameras and reflective markers.

Information on Research
You are being invited to participate in a study on how well your lungs work during exercise.

The purpose of this form is to give you information to help you decide if you want to take part in a research study. This consent form includes information about:
- Our reasons for using Optoelectronic Plethysmography to study breathing coordination during exercise.
- The things you will be asked to do while you are in the study.
- Any risks involved.
- Any potential benefits; and
- options other than taking part in the study, that you have.

The principal investigator, co-investigator or study coordinator will discuss the study with you. If at any time you have questions about the study please ask the study team. Take all the time you need to decide if you would like to take part in this research study.

The purpose of this research study is described below.

Why is this study being done?
We are doing this research study to compare the breathing coordination between trained cyclists and non trained individuals during exercise. We will be measuring this using a system called Optoelectronic Plethysmography.

You are being asked to take part in this study because you fit the criteria described below:
- Age 18-35
- You are a trained endurance athlete (is part of trained group)
- You are not a trained endurance athlete (if part of untrained group)
- No cardiovascular or pulmonary disease
- No neurological or musculoskeletal disease
- Free from injury
- No other health limitations that would stop him/her from being able to perform a cardiopulmonary exercise test.

What is involved in this study
We will be able to measure how the lungs expand and contract during exercise using cameras and reflective markers. We will place 89 of these reflective markers on your chest, back and abdomen. Then have you sit on a stationary bicycle. The amount each part of the chest moves will be calculated by these cameras and enter into a computer, this process is called Optoelectronic Plethysmography (OEP). You will perform a bike test and we will measure your breathing during exercise. You will be asked to exercise until your legs or breathing becomes too difficult to continue pedaling at the required speed.

Taking part in this study will last about 2 hours and you will be asked to visit with only one day.

Permission for future contact
The researchers may want to contact you for possible inclusion in future studies or to ask you questions regarding this experience.

Please initial below to show whether or not you give permission to be contacted in the future.

_____ (initial) I give permission to be contacted in the future for research purposes.

_____ (initial) I give permission to be contacted in the future for information regarding this study.

Risks
Potential Risks
Risks, side effects, or potential complications of the exercise test may include chest discomfort, headache, nausea, anxiety, tremor, a rise or fall in blood pressure, dizziness, irregular heart beat, shortness of breath, and fatigue. A very rare complication may include a heart attack or even death. Being a noninvasive measure of lung volume, the testing of respiratory mechanics using OEP

involves essentially no risks. Some subjects may experience mild discomfort with having to stand for a half hour while the markers are being places on the body. Mild skin irritation to tape adhesive may occur.

Benefits

Potential Benefits

The subjects may or may not benefit as a result of his/her participation in this study. Benefits may include a better understanding of his breathing mechanics, physical fitness and conditioning, and physical capacity to perform exercise. The data from the exercise test may allow for the athlete to adapt his training to better increase performance. The data from the OEP will allow for the subject to understand his breathing mechanics and possibly change his breathing techniques at peak exercise. Benefits to society may include a better understanding of how the different contributions of the chest cavity play a role in a person's ability to increase exercise tolerance. The analysis of how a untrained individual coordinates breathing compared to a trained may lead to better insight on how we can teach untrained people to breath more efficiently. Our findings may also lead to better analysis of the breathing techniques presently used in the fitness community and rehabilitation centers.

Alternative Procedures

This study is primarily to evaluate the breathing mechanics of endurance and non-endurance trained individuals using a new tool, OEP. The results obtained by this test will not affect any outcomes of your training or lifestyle.

You may refuse participation and in that case can have resting vitals monitored.

Confidentiality

All data will be held in the office of the principle investigator in Harkness Pavilion room 169b. The data will be kept under a random number code with the key held in the possession of the principle investigator. The office is locked and only accessible to the principle investigator and the researches involved in the study. Any use of the data will only be done with the random number code, and the data will be free of personal identifying information.

Research Related Injuries

There are no injuries associated with OEP.

During the exercise test we will closely watch you for any complications. Emergency equipment and trained staff are on hand to care for you if complications occur. However there are possibilities of chest discomfort, headache, nausea, anxiety, dizziness, heart palpitations, shortness of breath or tired legs. A very rare complication may include heart attack or death.

Please tell us if you are feeling any discomfort during the test.

Compensation

All subjects will have an exercise prescription assessment made based on their performance.

Repeated maximal exercise tests may given if desired, pre season, during training, and post season to determine if their exercise program was optimal.

Additional Costs

There are no additional costs.

Voluntary Participation

All participation is voluntary and there will be no repercussions to not participating in our study. If you refuse participate in our study, you are welcome to have your resting vitals taken.

Additional Information

Whom do I call if I have questions or problems?

If you have any questions or concerns about the study you may contact Dr. Matthew Bartels (212-305-0483), Aimee Layton (212-305-0483) or Renee Gerardo (212-305-9416).

If you have any questions about your rights as a research subject, you should contact the Columbia University Institutional Review Board by phone at (212) 305-5883 or by email at askirb@columbia.edu.

An Institutional Review Board is a committee organized to protect the rights and welfare of human subjects involved in research.

More information about taking part in a research study can be found on the IRB website at http://www.columbia.edu/cu/irb

Right to Withdraw

You have the right to withdraw from the study at any time. If you want to withdraw from the study during the interview or test you may tell the research staff and leave the room in which the study is taking place or by contacting Dr. Matthew Bartels (212-305-0483), Aimee Layton (212-305-0483) or Renee Gerardo (212-305-9416).

Statement of Consent

I have read the consent form and talked about this research study, including the purpose, procedures, risks, benefits and alternatives with the researcher. Any questions I had were answered to my satisfaction. I am aware that by signing below, I am agreeing to take part in this research study and that I can stop being in the study at any time. I am not waiving (giving up) any of my legal rights by signing this consent form. I will be given a copy of this consent form to keep for my records.

Signature

Study Subject
Print Name_____Signature_____Date_____

Person Obtaining Consent
Print Name_____Signature_____Date_____

Subject Name
Print Name_____

HIPAA Form A

HIPAA Clinical Research Authorization for Non-Sponsored Research

Protocol Number: IRB-AAAD5121
Name of Study: Chest Wall Kinematics during Maximum Exercise test in Elite Cyclist.
Principal Investigator: Matthew Bartels

For the purpose of the conduct of the above name study, I agree to permit Columbia University Medical Center, my doctors, and my other health care providers (together "Providers"), and Matthew Bartels and his/her staff (together "Researchers"), to use and disclose health information about me as described below.

1. **The health information that may be used and disclosed includes:**
   - all information collected during the research described in the Informed Consent Form for the above-named study ("the Research"); and
   - health information in my medical records that is relevant to the Research.
   - This may include medical history information that may be considered sensitive, including:

     Not Applicable

2. **The providers may disclose health information in my medical records to:**
   - the Researchers; and
   - representatives of government agencies, review boards, and other persons who watch over the safety, effectiveness, and conduct of research.

3. **The researchers may use and share my health information:**
   - among themselves and with other participating researchers to conduct the Research;
   - representatives of government agencies, review boards, and other persons who watch over the safety, effectiveness, and conduct of research; and
   - as permitted by the Informed Consent Form.

4. **Please note that:**
   - You do not have to sign this Authorization, but if you do not, you may not participate in the Research.
   - You may change your mind and revoke (take back) this Authorization at any time and for any reason. To revoke this Authorization, you must write to Privacy Officer, Columbia University, 601 West 168th Street, Apt. 22, New York, N.Y. 10032. However, if you revoke this Authorization, you will not be allowed to continue taking part in the Research. Also, even if you revoke this Authorization, the Researchers may continue to use and disclose the information they have already collected as permitted by the Informed Consent Form.
   - While the Research is in progress, you may not be allowed to see your health information that is created or collected by Columbia University in the course of the Research. After the Research is finished, however, you may be allowed to

see this information.

5. This Authorization does not have an expiration (ending) date.

6. You will be given a copy of this Authorization after you have signed it.

Printed Name of Subject: _____

Signature of Subject or Legal Representative: _____ Date: _____

Relationship of Legal Representative to Subject (if applicable): _____

APPENDIX D

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APPENDIX E

Chapter IV.

I. Pre-test questionnaire

PRE-TEST MEDICAL HISTORY QUESTIONNAIRE

Name: _____

Date of Birth: _____ Height: _____ Weight: _____ Gender: _____

What endurance exercise do you perform? _____

Do you compete in your sport? _____ If so, for how many years? _____

How many hours per week? _____ Or how many miles per week? _____

Please Indicate if you have any of the following (please check the box):

	Yes	No
Pain or discomfort in the chest with exercise		
Wheeze or cough		
Atopy or allergies that effect breathing		
Excessive mucus production with exercise		
Asthma or bronchitis		
Strider or vocal cord discomfort		
Chest surgery		
Heart Disease		
Lung Disease		
Palpitations or awareness of heartbeat		
Arrhythmia or irregular heartbeat		
Rheumatic fever		
Heart murmur		
Diabetes Mellitus		
High cholesterol or high triglycerides		
Previous cardiac stress test		

Do you have any medication allergies? _____ If so, which medications? _____

Are you taking any medications, including inhalers? _____ If yes, please list them:

Medication Name	Dose	Frequency

Date of your last menstrual cycle: _____

Do you believe you are pregnant or have had a baby in the last 3 months? _____

Institutional Review Board (IRB)
IRB # AAAI1741 Approval Date 01.10.12
Initials SL Expiration Date 01.09.13
Columbia University Medical Center

TEACHERS COLLEGE, COLUMBIA UNIVERSITY
INSTITUTIONAL REVIEW BOARD
Protocol # 12-148
Consent form approved until 3/7/2013
IRB Signature SH/MB

II. Modified Borg Scale

Rating Perceived Exertion – Modified Borg Scale	
0	**Nothing at all**
0.5	**Very, very slight (just noticeable)**
1	**Very slight**
2	**Slight**
3	**Moderate**
4	**Somewhat severe**
5	**Severe**
6	
7	**Very severe**
8	
9	**Very, Very severe (almost maximal)**
10	**Maximal**
Reprinted Circulation 1995; 91(2). P.586.	

III. Recruitment Flyer

We Need Female Cyclist and Tri-athletes for a Research Study!

Institutional Review Board (IRB)
IRB # AAAI1741 Approval Date 01.10.12
Initials SI Expiration Date 01.09.13
Columbia University Medical Center

WHY?

- To learn more about possible breathing limitations female athletes may have during their competitions.

WE NEED YOU IF:

- A competitive female cyclist or tri-athlete.
- You train greater than 10hrs a week or greater than 50 miles of cycling.
- You are between 18-50 yrs old

THE RESEARCH:

- Is three exercise tests on two separate days:
  - 1st- a VO2 max test to test your fitness level.
  - 2nd- two endurance tests for 10 min where we measure your breathing mechanics using motion analysis.

YOU GET:

VO2 Max results and Exercise Prescription worth $500!

Please contact Aimee Layton @ AML2135@columbia.edu or (212) 305-0483

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We Need Female Cyclist and Tri-athletes for a Research Study!

WHY?

- To learn more about possible breathing limitations female athletes may have during their competitions.

WE NEED YOU IF:

- A competitive female cyclist or tri-athlete.
- You train greater than 10hrs a week or greater than 50 miles of cycling.
- You are between 18-50 yrs old

THE RESEARCH:

- Is three exercise tests on two separate days:
  - 1st- a maximal aerobic capacity test (otherwise known as a VO2 max test) to test your fitness level.
  - 2nd- two endurance tests for 10 min where we measure your breathing mechanics using motion analysis.

YOU GET: VO2 Max results and Exercise Prescription a $500 value

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IV. Consent Form

Columbia University Medical Center Consent Form

Attached to Protocol: IRB-AAAI1741
Principal Investigator: Carol Garber
(ceg2140)
IRB Protocol Title: Effects of Expiratory Flow Limitations on Ventilatory Mechanics and Dyspnea in Female Endurance Athletes

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INSTITUTIONAL REVIEW BOARD
Protocol # 12-148
Consent form approved until 3/7/2013
IRB Signature

Consent Number: **CF-AAAK2456**
Participation Duration: 1 to 2 hrs
Anticipated Number of Subjects: 65

Contact

Contact	Title	Contact Type	Numbers
Aimee Layton	Clinical Coordinator	Co-Investigator	Telephone: 212-305-0483 Cell: 201-602-9849

Research Purpose
The general purpose of this study is to determine if female endurance athletes with expiratory flow limitations (EFL) have altered ventilatory mechanics, increased dynamic hyperinflation of chest wall volumes (DH) and increased dyspnea when compared to female endurance athletes with no EFL.

Information on Research
We are doing this research study to find out if female athletes have something called expiratory flow limitations, which means they have trouble getting air out of their lungs when they are exercising very hard. We are also looking to find out if the athletes with expiratory flow limitations have more shortness of breath and a change in how their breathing muscles move air to accommodate the flow limitation. You are being asked to take part in this study because you are a woman who participates in competitive endurance sports that involve cycling. We ask that you are a cyclist because the tests are performed on a stationary bicycle. 65 people are expected to be enrolled in this study here at Columbia University Medical Center.

The purpose of this form is to give you information to help you decide if you want to take part in a research study. This consent form includes information about: - why the study is being done; - the things that you will be asked to do if you are in the study; - any known risks involved; - any potential benefit; and - options, other than taking part in this study, that you have. The principal investigator (the lead researcher for this project) will discuss the study with you. If at any time you have questions about the study, please ask a member of the study team. Take all the time you need to decide whether you want to take part in this research study. The purpose of this research is described below in the 'What is Involved in This Study?' section of this consent form.

Taking part in this study will last 1-2 hrs and will include 2 visits. The schedule of study visits and the procedures that will be done at each visit are as follows:

Columbia University IRB
IRB Approval Date: 01/19/2012
for use until: 01/09/2013

The first study day will consist of breathing tests, an exercise test and an ultrasound test in the laboratory. All three tests will take no longer than 2 hrs. Before exercise we will have you perform a few breathing tests that will tell us all about your lungs and how they move air. These tests take effort but do not hurt.

After the breathing tests you will have a seat on a stationary bicycle.We will be monitoring your heart with stickers call "electrodes", your blood pressure with a cuff on your arm, your oxygen with a light on your finger and breathing with a mouthpiece in your mouth. None of these things should hurt but may be slightly uncomfortable. There will be no needles or invasive procedures.

You will start with 5 minutes of resting on the bike so we can see how your body is before exercise. Then we will have a 3 minute "warm-up" of very easy pedaling. After 3 minutes resistance will start to accumulate on the pedals. You continue exercise for as long as you can but the test is designed to only last about 10-15 minutes once the resistance stage begins. When you feel you are too tired and can not keep pedaling at a cadence of 70-80 rpm, you hold up a finger to indicate you would like to stop in a minute. We will coach you through that minute and then take all of the resistance off and you will perform an easy "cool down". If you can not give a one minute warning and would like to stop just slow down your pedaling below 50 rpm and we will know you are too tired and will take the resistance off the pedals. If at anytime you are not feeling well, such as dizziness, nausea, chest pain or any other symptom that you think is unusual, please take the mouthpiece out of your mouth and tell us and we will have you stop exercising. If we see any reason for you to stop exercising we will tell you and stop the test.

Before or After your maximal exercise test, we will ask you if you mind having an ultrasound of your trachea performed. It does not hurt and consists of having some cool hypoallergenic gel placed on your neck. Then the doctor will lightly run a wand over your neck to measure your trachea size. This will not hurt and has no known risks associated with it, it will take about ten minutes and can be performed before or after your exercise test at your convenience.

At your second visit you will have 2 exercise tests performed with optoelectronic plethysmography (OEP).

OEP will consist of having 89 reflective dots placed on your chest, stomach and back. You will have to have your shirt off for this test but you may wear a sports bra or regular bra. The dots will not hurt and will take about 10 minutes to apply to your body.

Once OEP is set up, we will have you sit on a stationary bicycle with your arms at your side holding onto side handle bars so that your limbs to not infer with the infra red cameras that measure the dots moving. These cameras do not record you, only the dots.

The exercise tests will begin with 3 minutes of warm-up pedaling and then either 40% of the peak resistance you obtained during the maximal test will be applied to the pedals or 85% of the maximal work load you obtained during you maximal test will be applied to the pedals. We will decide this by flipping a coin. You will exercise at this level for 10 minutes or until you are too tired. If you would

like to stop before 10 minutes is over please indicate by slowing down you pedaling below 50 rpms.

In between the exercise tests you will be encouraged to drink water or a drink that you have brought with you. There will be 30 minutes in between exercise tests. During this time we ask that you remain lightly pedaling on the bike so that your muscles stay warm. After the 30 minutes you will perform either the 40% or 85% workload protocol depending on which test you performed first. You may decide to not continue exercise at anytime during this session. The session will last about an hour to 2 hours.

Risks

There may be general risks or discomfort if take part in this study. These include: chest discomfort, headache, nausea, anxiety, tremor, a rise or fall in blood pressure, dizziness, irregular heartbeat, shortness of breath, and fatigue. A very rare complication may include a heart attack or even death. A code cart and rescue inhalers will be present. All testing personnel are certified in Advanced Cardiac Life Support and Basic Life support training.
Being a noninvasive measure of lung volume, the testing of respiratory mechanics using OEP involves essentially no risks. No risks to having the markers placed on the skin have been reported. There may be other risks associated with the study that we don't know about. If we learn about other risks, we will let you know what they are so that we can decide whether or not you want to continue with the study.

Benefits

The subjects may or may not benefit as a result of her participation in this study. Benefits may include a better understanding of her breathing mechanics, physical fitness and conditioning. The data from the exercise test may allow for the athlete to adapt her training to better increase performance. The data from the OEP will allow for the subject to understand her breathing mechanics.

Alternative Procedures

As an alternative you may choose to not take part in this study.

Confidentiality

Any information collected during this study that can identify you by name will be kept confidential. We will do everything we can to keep your data secure, however, complete confidentiality cannot be promised. Despite all of our efforts, unanticipated problems, such as a stolen computer may occur, although it is highly unlikely. To maintain confidentiality all records will be kept in a locked file that only study personnel will have access too. Your tests will be kept on a password protected system and not shared with outside study personnel. The results of your exercise test results will not be shared with any non-study member.
The following individuals and/or agencies will be able to look at and copy your research records: - The investigator, study staff and other medical professionals who may be evaluating the study - Authorities from Columbia University and New York Presbyterian Hospital, including the Institutional Review Board (IRB).

TEACHERS COLLEGE, COLUMBIA UNIVERSITY
INSTITUTIONAL REVIEW BOARD
Protocol # 12-148
Consent form approved until 3/7/2013
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Columbia University IRB
IRB Approval Date: 01/19/2012
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Compensation

For your time, we will provide you with an assessment of your fitness level and an exercise prescription based on the results.
There will be no monetary compensation.

Voluntary Participation

Taking part in this study is your choice. You can decide not to take part in or stop being in the study at any time. Your choice will not affect the treatment you receive from doctors and staff at Columbia University Medical Center and New York Presbyterian Hospital.

Additional Information

Contact Information

Who do I call if I have a problem or question?
Questions If you have any questions or are hurt while taking part in this research study, you should contact Aimee Layton, (212)305-0483, aml2135@columbia.edu, 622 W 168th St. VC3-365, NY, NY 10032.
If you have any questions about your rights as a research subject, you should contact the Columbia University Institutional Review Board by phone at (212) 305-5883 or by email at irboffice@columbia.edu. More information about taking part in a research study can be found on the Columbia University IRB website at: http://www.cumc.columbia.edu/dept/irb.

Statement of Consent

Statement of consent I have read the consent form and talked about this research study, including the purpose, procedures, risks, benefits and alternatives with the researcher. Any questions I had were answered to my satisfaction. I am aware that by signing below, I am agreeing to take part in this research study and that I can stop being in the study at any time. I am not waiving (giving up) any of my legal rights by signing this consent form. I will be given a copy of this consent form to keep for my records.

Signature

Study Participant
Print Name_____ Signature_____ Date_____

Person Obtaining Consent
Print Name_____ Signature_____ Date_____

TEACHERS COLLEGE, COLUMBIA UNIVERSITY
INSTITUTIONAL REVIEW BOARD
Protocol # 12-148
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IV. HIPPA Form

HIPAA Form A

HIPAA Clinical Research Authorization for Non-Sponsored Research

Protocol Number: IRB-AAAI1741
Name of Study: Effects of Expiratory Flow Limitations on Ventilatory Mechanics and Dyspnea in Female Endurance Athletes
Principal Investigator: Carol Garber

For the purpose of the conduct of the above name study, I agree to permit Columbia University Medical Center, my doctors, and my other health care providers (together "Providers"), and Carol Garber and his/her staff (together "Researchers"), to use and disclose health information about me as described below.

1. **The health information that may be used and disclosed includes:**
   - all information collected during the research described in the Informed Consent Form for the above-named study ("the Research"); and
   - health information in my medical records that is relevant to the Research.
   - This may include medical history information that may be considered sensitive, including:

     not applicable

2. **The providers may disclose health information in my medical records to:**
   - the Researchers; and
   - representatives of government agencies, review boards, and other persons who watch over the safety, effectiveness, and conduct of research.

3. **The researchers may use and share my health information:**
   - among themselves and with other participating researchers to conduct the Research;
   - representatives of government agencies, review boards, and other persons who watch over the safety, effectiveness, and conduct of research; and
   - as permitted by the Informed Consent Form.

4. **Please note that:**
   - You do not have to sign this Authorization, but if you do not, you may not participate in the Research.
   - You may change your mind and revoke (take back) this Authorization at any time and for any reason. To revoke this Authorization, you must write to Privacy Officer, Columbia University, 601 West 168th Street, Apt. 22, New York, N.Y. 10032. However, if you revoke this Authorization, you will not be allowed to continue taking part in the Research. Also, even if you revoke this Authorization, the Researchers may continue to use and disclose the information they have already collected as permitted by the Informed Consent Form.
   - While the Research is in progress, you may not be allowed to see your health information that is created or collected by Columbia University in the course of the Research. After the Research is finished, however, you may be allowed to

TEACHERS COLLEGE, COLUMBIA UNIVERSITY
INSTITUTIONAL REVIEW BOARD
Protocol # 12-148
Consent form approved until 3/7/2013
IRB Signature

see this information.

5. **This Authorization does not have an expiration (ending) date.**

6. **You will be given a copy of this Authorization after you have signed it.**

Printed Name of Subject: _____

Signature of Subject or Legal Representative: _____ Date: _____

Relationship of Legal Representative to Subject (if applicable): _____

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INSTITUTIONAL REVIEW BOARD
Protocol # 12-148
Consent form approved until 3/7/2013
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V. Coaches or Captain letter

COLUMBIA UNIVERSITY
MEDICAL CENTER

Human Performance Laboratory
622 W168th St.VC3-337
New York, NY 10032

Dear Coach or Captain,

We are conducting an exercise research study at Columbia University Medical Center-New York Presbyterian Hospital and are interested in recruiting female cyclists and tri-athletes to participate.

This study is investigating the breathing mechanics of female endurance athletes during vigorous exercise.

The study will consist of two visits that will be approximately 1-2 hrs. The first visit will consist of a "VO2 Max" test to tell us the athlete's maximum fitness level and anaerobic threshold. The second visit will entail two endurance tests of approximately 10 minutes in duration with a 30 min light pedaling in between where we will analyze the breathing mechanics of the athlete using motion analysis.

There are no needles or invasive measures. For volunteering their time, athletes will be given an analysis of their VO2 max results along with a personalized training plan that includes the amount of calories they burn at each intensity level.

If you could please forward this letter to your female athletes we would be greatly appreciated.

Many thanks,

Aimee Layton

Email: aml2135@columbia.edu

Phone: (212) 305-0483