CHEST WALL RESTRICTION CAUSES DIAPHRAGM FATIGUE IN LOW INTENSITY EXERCISE

by

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ABSTRACT

Artificially induced chest wall restriction (CWR) has been used in numerous studies as a model of restrictive lung disease, as CWR has been shown to mimic the breathing mechanics of such conditions. Fast, shallow breathing, reduced resting and operational lung volumes and a greater work of breathing than unrestricted controls characterizes CWR. Diaphragm fatigue has been shown to occur in healthy humans exercising at very high intensities until volitional fatigue. A high work of breathing is associated with diaphragm fatigue, however, to date there have been no investigations examining the relationship between CWR and diaphragm fatigue. Accordingly the purpose of this study was to examine the relationship between diaphragm fatigue in CWR subjects exercising at low intensities. It was hypothesized that exercise at 45% of VO_{2MAX} with chest wall restriction would result in a higher work of breathing and significant diaphragm fatigue compared to unrestricted exercise. The work of breathing was determined by averaging the area under the transpulmonary pressure-volume curve for 8-10 breaths during exercise. Diaphragm fatigue was assessed by performing a series of non potentiated and potentiated twitches, before exercise, 10 and 30 minutes after control exercise and at 10, 30 and 60 minutes after CWR exercise. The average amplitude of the transdiaphragmatic pressure (Pdi) from the different groups of twitches was compared using a repeated measures one-way ANOVA. Post-hoc analysis was done using multiple t-tests with a Bonferonni correction. A total of 7 men gave informed consent and participated in this study. All subjects showed a significantly higher work of breathing in the CWR exercise compared to the control exercise at the 8^{th} and 10^{th} minute (At the 8^{th} minute CWR = 720 $\pm$ 159cmH_2O/min vs. control = 536 $\pm$ 151cmH_2O/min and at the 10^{th} minute CWR = 796 $\pm$ 216cmH_2O/min vs. control = 566 $\pm$ 136cmH_2O/min, $p < 0.05$). Five of the 7 subjects showed a greater than 15% drop in twitch Pdi 10 minutes post exercise, indicating diaphragm fatigue. The twitch Pdi post CWR exercise was significantly less than baseline for the potentiated twitches (36.5 $\pm$ 15.3 cmH_2O vs. 47.4 $\pm$ 16.6 cmH_2O, $p < 0.01$) and for the non potentiated twitches (24.6 $\pm$ 8.5 cmH_2O vs. 30.7 $\pm$ 8.6 cmH_2O, $p < 0.05$). Furthermore, the percent drop in twitch Pdi after CWR exercise was correlated to the elastic work of breathing on inspiration ($R^2 = 0.73992$, $p < 0.05$). The resting and operational lung volumes were significantly reduced in all subjects in the

CWR condition compared to the control condition and all subjects showed a tachypneic breathing pattern throughout the CWR exercise. Expiratory flow limitation towards the end of the CWR exercise was present in all subjects and 3 of the 7 subjects showed dynamic hyperinflation. This data suggests that CWR reduces lung volumes and alters the breathing mechanics, to the degree of causing diaphragm fatigue after low intensity exercise. The diaphragm fatigue is likely attributed to the high work of breathing and reduced lung volumes.

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LIST OF ABBREVIATIONS

CWR = Chest wall restriction

FVC = Forced vital capacity

FEV_1 = Forced expiratory volume in one second

TLC = Total lung capacity

RV = Residual volume

FRC = Functional residual capacity

IRV = Inspiratory reserve volume

Pdi = Transdiaphragmatic pressure

Pga = Gastric pressure

Poes = Oesophageal pressure

Pm = Mouth pressure

EFL = Expiratory flow limitation

MIP = Maximal inspiratory pressure

MFVL = maximal flow volume loop

I (res) = Inspiratory resistive work of breathing

E (res) = Expiratory resistive work of breathing

I (el) = Inspiratory elastic work of breathing

VO_{2MAX} = Maximal oxygen consumption

$PetCO_2$ = End tidal CO_2

SaO_2 = Oxygen saturation

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INTRODUCTION

Chest wall restriction (CWR) induces a reduction in compliance of the thoracic wall and consequently alters breathing mechanics. In unrestricted healthy humans the chest wall expands upon inhalation, and recoils upon exhalation, however, in people with CWR the ability to expand the chest wall is limited. Changes in breathing mechanics, in turn, contribute to altered breathing patterns, reduced static and operational lung volumes, and an increased work of breathing. Chest wall restriction occurs in individuals with conditions such as kyphoscoliosis, pectus excatvatum, ankylosing spondlitis, pleural disease, neuromuscular disease, abdominal distention, chest wall paralysis, interstitial lung disease, chronic heart failure and obesity (Cline et al., 1999; Coast and Cline, 2004; Miller et al., 2002; O'Donnell et al., 2000). Individuals with these conditions typically have low exercise tolerance and often experience dyspnea during activities of daily living (Johnson et al., 2000; O'Donnell et al., 1998 and 2000).

External physical restriction devices have been used on healthy individuals to reduce compliance in an attempt to mimic restrictive mechanical abnormalities of the chest wall (Cline et al., 1999; Coast and Cline, 2004; Harty et al., 1999; Hussain et al., 1985; Miller et al., 2002; O'Donnell et al., 2000). Specifically, studies by Miller et al. (2002), and O'Donnell et al. (2000), have examined breathing mechanics through the measurement of lung volumes, breathing patterns and the work of breathing in CWR subjects. In 2002, Miller et al. induced CWR in healthy humans and showed a 33% reduction in total lung capacity (TLC) and a 38% reduction in vital capacity (VC). Chest wall restricted subjects had an average forced vital capacity (FVC) of 3.66 liters compared to an FVC of 5.79 liters in an unrestricted condition. They also found that residual volume (RV) in CWR subjects was reduced by 23%. Using a similar method of CWR, O'Donnell et al. (2000), found comparable reductions in FVC (35 $\pm$ 2%) primarily due to decreases in TLC, however, reductions in RV were not found. Furthermore, Miller et al., also showed that end expiratory lung volume (EELV) was reduced in CWR subjects both at rest and during exercise at 25% of maximal aerobic capacity (VO_{2MAX}), however, during exercise at 45% VO_{2MAX} an upward shift in EELV occurred. This upward shift allowed subjects to access higher flow rates, preventing expiratory flow limitation (EFL). O'Donnell et al., also showed decreased inspiratory capacity (IC) (36 $\pm$ 2%) in CWR subjects, which was attributed to reductions in TLC and functional residual capacity (FRC). As well, significant reductions in inspiratory reserve volume (IRV) were shown, indicating that the reserve volume available to further increase the volume of tidal inspirations was significantly reduced (O'Donnell et

al., 2000). It is this reduction in IC and IRV that leads to the rapid and shallow breathing pattern seen with CWR, as demonstrated by an increased tidal volume (V_T) to IC (V_T/IC) ratio during submaximal exercise (O'Donnell et al., 2000).

The breathing patterns of healthy individuals are altered when restriction is applied; V_T is reduced at rest and cannot be increased during exercise due to the limitations imposed by reductions in IRV (O'Donnell et al., 2000). This leads to greater breathing frequencies, with minimal enlargements in V_T during exercise and has been shown to occur even at low exercise intensities (25% and 45% VO_{2MAX}) (Miller et al., 2002). Furthermore, this rapid shallow breathing pattern is present in individuals with restrictive lung disease (Johnson et al., 2000) and is associated with enhanced sensations of dyspnea during exercise and may play a role in exercise intolerance. O'Donnell et al., (2000) has shown that in the presence of CWR the intensity of dyspnea is significantly greater at any given exercise load. It was reported that subjects described their sensations of dyspnea as "I cannot get enough air in," "I cannot take a deep breath" and other descriptors of "inspiratory difficulty" or "unsatisfied inspiration."

Chest wall restriction increases the work of breathing (WOB), which could potentially contribute to exercise intolerance. In CWR the limited capacity to expand the thoracic space forces the diaphragm and other muscles of inspiration to generate greater force in order to produce inhalation (Miller et al., 2002). Transdiaphragmatic pressure (Pdi) is the difference between oesophageal (Poes) and gastric pressure (Pga) and is used as an indication of the force output of the diaphragm. During inhalation in quiet breathing, the Pdi increases approximately 10 cmH_2O. However, during exercise, and in restrictive lung disease, the Pdi upon inhalation may reach values of up to 100-150 cmH_2O (Banner, 1995). Miller et al. (2002), showed that the time integral of Pdi ($\int$Pdi*s) is significantly greater in CWR subjects at rest (866 $\pm$ 474 cmH_2O*s) and when exercising at 45% of VO_{2MAX} (1441 $\pm$ 76 $cmcH_2O$*s) compared to unrestricted control subjects at rest (247 $\pm$ 71 $cmcH_2O$*s) and at 45% of VO_{2MAX} (371 $\pm$ 56 cmH_2O*s). This emphasizes that in order to produce the same ventilatory rate in CWR subjects compared to controls the diaphragmatic work is much higher.

The total work of breathing is the sum of the flow resistive and elastic work of breathing (Hlastala and Berger, 1996). When the work of breathing is partitioned into flow resistive work and elastic work, Miller et al. showed that CWR subjects exercising at 45% of VO_{2MAX} experienced a significantly greater flow resistive work of breathing (1416 $\pm$ 777 L*cmH_2O /min) compared to

unrestricted controls (883 $\pm$ 340 l*cmH_2O/min) ($p < 0.01$). The elastic work of breathing, however, was significantly reduced (473 $\pm$ 228 l*cmH_2O/min) in CWR subjects compared to unrestricted control subjects (669 $\pm$ 263 l*cmH_2O/min) ($p < 0.01$). This resulted in modest increases in the total work of breathing during exercise at 45% of VO_{2MAX}. These changes in the work of breathing are attributed to reduced lung volumes associated with CWR. Flow resistive work increases at low lung volumes as the airways are compressed, and the elastic work of breathing increases at really low lung volumes and high lung volumes. Therefore, the lung volume where the work of breathing is at a minimum is near FRC. Individuals with restrictive lung diseases, like CWR subjects, breathe at lower lung volumes and have a reduced FRC. Breathing at lower lung volumes reduces the elastic work of breathing, but consequently increases the resistance to flow and the flow resistive work of breathing (Olson et al., 2006). Increases in the work of breathing in CWR may enhance the likelihood of diaphragm fatigue, however, the phenomenon of diaphragm fatigue has not been investigated in CWR subjects.

Skeletal muscle fatigue is defined as "a condition in which there is a loss in capacity for developing force and/or velocity of a muscle resulting from muscular activity under a load and which is reversible by rest" (National Heart Lung and Blood Institute Workshop 1990). Fatigue of the diaphragm has been shown to occur in healthy individuals exercising at intensities of 80-85% VO_{2MAX} until exhaustion (Babcock et al., 1995; Dempsey et al., 2006; Johnson et al., 1993; Romer and Polkey, 2008). In CWR subjects, much larger inspiratory pressures must be generated and consequently, the work of breathing and the work of the diaphragm increases. It is therefore possible that the diaphragm may also fatigue at relatively low exercise intensities under CWR conditions compared to unrestricted conditions.

To further our understanding of the complexities that govern exercise intolerance and dyspnea in patients with restrictive lung disease, it is important to examine the mechanisms of diaphragm fatigue as a potential contributing factor. However, it is difficult to conduct research in this population group due to the presence of other co-morbidities and severe exercise intolerance. Applying CWR to healthy individuals will eliminate any potential pathological conditions and provide a model of restrictive lung disease allowing for the investigation of diaphragm fatigue. While other studies have examined the effects of CWR on lung volumes, breathing patterns, sensations of dyspnea and the work of breathing, none have examined the effect of CWR on diaphragm fatigue. This leads to the primary question of this thesis; does diaphragm fatigue occur in healthy CWR

subjects exercising at 45% of VO_{2MAX}? An intensity of 45% of VO_{2MAX} was chosen for this study as this is the intensity at which subjects exercised in the Miller et al., (2002) CWR study, and therefore, the result that were found in this study could be compared to what has previously been shown.

HYPOTHESIS

It is hypothesized that individuals exercising at an intensity of 45% of VO_{2MAX}, for ten minutes, in the presence of chest wall restriction will experience a significantly higher work of breathing and diaphragm fatigue ten minutes after the completion of exercise, compared to when exercising in an unrestricted control trial.

METHODS

SUBJECTS

Eight male subjects (21-39 years of age) provided written informed consent to participate in this study, however, one subject was excluded from the analysis based on faulty balloon placement. Subjects were excluded if they had a previous history of asthma, smoking or cardiopulmonary disease. They were also excluded if they had a cardiac pacemaker, any metal inside their bodies, if they had an oesophageal ulcer or tumour or if they have had nasopharyngeal surgery.

EXPERIMENTAL PROTOCOL

All data collection took place in the Health and Integrative Physiology Laboratory at the University of British Columbia. Procedures were approved by the Clinical Research Ethics Board of the University of British Columbia for Research and Other Studies Involving Human Subjects. Testing consisted of two testing days. The first day was comprised of a maximal aerobic test on a cycle ergometer and also served to familiarize the subjects with all the test protocols. The second day served as an experimental day. On the first day, testing procedures were explained and informed consent was obtained. Anthropometric measures and basic pulmonary function tests were performed. Subjects were familiarized with the use of cervical magnetic stimulation and chest wall restriction ensuring their ability to tolerate the testing procedures. Seven stimulations to the back of the neck were given to the subjects with the magnetic stimulator at 30, 50, 60, 70, 80, 90 and 100% of stimulator output. As well, the chest wall restriction straps were put on the subject and tightened as they exhaled to RV. The subjects then cycled, with the straps on, at a relatively low intensity for three minutes. After being familiarized to these procedures an incremental cycle test to exhaustion was completed to determine maximal aerobic power (VO_{2MAX}) and peak power output. The results were used to determine the exercise intensity for the subsequent test day.

On the experimental testing day subjects had two balloon tipped catheters inserted; one placed inside the oesophagus to measure Poes and one placed in the stomach to measure Pga. Pdi could then be measured as the difference between Pga and Poes and represents the force output of the diaphragm. Surface electromyography (EMG) electrodes were placed over their intercostal muscles in their 7-9th rib space to record electrical activity from the diaphragm. A series of maximal diaphragm twitches were performed in order to establish the baseline amplitude of the Pdi twitch response and were used for future comparisons with post exercise twitch Pdi values.

Following the collection of baseline twitch Pdi subjects underwent two bouts of cycle exercise at 45% of VO_{2MAX} for 10 minutes. This intensity was chosen in order to facilitate comparisons with other CWR and exercise studies in which subjects performed CWR exercise at an intensity of 45% of VO_{2MAX} (Miller et al., 2002). The control exercise and CWR exercise were separated by approximately 40 minutes and the collection of two sets of Pdi data. Twitches were collected at 10 and 30 minutes post control exercise and were analyzed to ensure that the amplitude of the twitch Pdi showed no signs of fatigue before the second exercise bout was completed. In one subject additional twitches were completed at 60 minutes post control exercise as the amplitude of their twitch Pdi had not returned to baseline levels at the 30 minute mark. In another subject twitches were not done at 30 minutes post control exercise, as it was evident in the twitches at 10 minutes post that the subject showed no signs of fatigue. Later investigation of the twitches showed that all subjects, except one, did not differ from baseline 10 minutes after the control exercise.

Following the CWR exercise, the straps were removed and twitch Pdi was assessed 10, 30 and 60 minutes post exercise. A drop in post exercise Pdi > 15% from baseline Pdi was indicative of diaphragm fatigue (NHLBI Workshop Summary 1990). During both exercise bouts, operational lung volumes, the work of breathing, respiratory pressures and ventilatory parameters were monitored.

MEASUREMENTS

Pulmonary Function Testing

Subjects performed pulmonary function testing using a spirometer as per standardized procedures (American Thoracic Society/European Respiratory Society, 2002). On the familiarization day, forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow rate (PEF) and maximum voluntary ventilation (MVV) were measured using a portable spirometer (Spirolab II, Medical International Research, Vancouver BC). Subjects also performed several inspiratory capacity (IC) maneuvers from functional residual capacity (FRC) until they were able to reproduce the measurement.

Pulmonary function testing was also performed on the experimental day without CWR and again once the CWR straps were in place to ensure that the application of the CWR straps had achieved a 40% reduction in FVC. If the degree of restriction was less than 40% the straps were removed and reapplied until at least a 40% reduction in FVC was achieved.

Peak Exercise Test

Maximal aerobic power was determined using a ramp exercise test on an electronically braked cycle ergometer (Excalibur Sport, Lode, Gronigen, Netherlands). The test began at a workload of 0 Watts and increased 30 Watts every minute until volitional fatigue. To determine VO_{2MAX} subjects wore nose clips and breathed through a mouthpiece connected to a heated pneumotach (model 3812, Hans Rudolph, Kansas City, MO). Mixed expired gases were collected in a mixing chamber and were measured using CO_2 and O_2 analyzers (Model CD-3A and Model S-3A/I respectively, AEI Technologies Applied Electrochemistry, Pittsburgh, PA). Metabolic data was recorded at 200 Hz (PowerLab/16SP model ML 795, ADI, Colorado Springs, CO) and stored on a computer for subsequent analysis (Chart v6, ADInstruments, Colorado Springs, CO). Volume was obtained by integrating the flow signal. Heart rate was measured using a commercially available heart rate monitor (Polar Electro, Kempele, Finland) and recorded every minute during exercise. Oxygen saturation (SaO_2) was measured using a finger pulse oximeter (Criticare Systems Inc., 504 Serirs, Waukesha, WI) and recorded every minute. Ratings of perceived exertion (RPE) were also recorded for leg discomfort and dyspnea every minute. The maximal power achieved in the test was used to determine the work load (45% of maximal power output) for the exercise bouts on the second experimental test day. The test was terminated when the subject was no longer able to maintain 60 revolutions per minute.

Cervical Magnetic Stimulation

Exercise induced diaphragm fatigue was assessed by comparing maximal twitch Pdi before and after exercise. A drop of 15% or greater in twitch Pdi post exercise was indicative of diaphragm fatigue (ATS/ERS, 2002). Twitch Pdi was assessed using CMS before and after both the control and CWR exercise. The CWR straps were removed in order to complete the CMS. Cervical magnetic stimulation involved the use of a magnetic coil to create a pulsed magnetic field. When the coil was placed near conductive tissues it induced an electrical field. The electrical field created a current and if the amplitude and duration of the electrical field were appropriate, neuromuscular tissues could be stimulated (Similowski et al., 1989).

In this study a stimulation unit with a 90 mm coil and a center hole was used to perform the CMS (Magstim 200, Mono Pulse MagStim Whitland, Wales). The phrenic nerve roots (C3-C5) were

stimulated with the coil placed in the midline between the C5-C7 spinous processes. The spinous process of C7, which is large, easily seen and palpated, was used to landmark the initial location of the stimulator (Glerant et al., 2006; Laghi et al., 1996; Mador et al., 2002; Similowski et al., 1989; Similowski et al., 1997; Wragg et al., 1994). To determine the location where the largest twitch Pdi was achieved, stimulations were given moving up and down the midline from C5 to C7. Once the location was established it was marked with a bright marker and all further stimulations were given in the same location (Laghi et al., 1996; Mador et al., 2002; Similowski et al., 1989; Similowski et al., 1997; Wragg et al., 1994).

Cervical magnetic stimulation was conducted prior to exercise, to determine baseline maximal Pdi, and again 10 and 30 after the control exercise and 10, 30 and 60 minutes after the CWR exercise. Before baseline measures were taken the subject underwent a ramp protocol in which the power output of the magnetic stimulator was gradually increased. This was necessary to ensure the subject was supramaximally stimulated by the CMS. Supramaximal stimulation was indicated by a plateau in the twitch Pdi with increasing power output from the magnetic stimulator (Mador et al., 1996a, Mador et al., 1996b). Prior to the ramp protocol three twitches were done at 100% of stimulator power output. The ramp was composed of three twitches at 50, 60, 70, 80, 85, 90, 95 and 100% of stimulator power output. All twitches were separated by 30 seconds in order to minimize the possibility of twitch potentiation (Taylor et al., 2006). The amplitude of the twitches at 100% of stimulator power output prior to the ramp were compared to the final three twitches at 100% to ensure that the twitches did not become potentiated. Following the ramp protocol and ten minutes of rest (necessary to ensure there was no abnormal diaphragmatic activity), each subject underwent eight non-potentiated twitches and five potentiated twitched to determine the amplitude of their baseline twitch Pdi.

Non Potentiated Twitch

In each set of twitches (before and 10 and 30 minutes post control exercise, as well as 10, 30 and 60 minutes post CWR exercise), eight non potentiated twitches were delivered at 100% of stimulator power output. All twitches were separated by at least 30 seconds to prevent potentiation. Subjects were given the instruction “at the end of a normal breath out stick up your thumb”, and when the subject stuck their thumb up the stimulation was delivered. As changes in lung volume can affect the contractility of the diaphragm, the Poes trace was monitored during the twitch protocol to

ensure the subject was at the end of a normal breath out (FRC) when the twitch was delivered and that they had not changed their breathing pattern in anticipation of the twitch (Mador et al., 2002; Taylor et al., 2006). FRC was indicated by the Poes = ~ -5cmH_2O, if this did not occur than the twitch was redone and not included in analysis.

Potentiated Twitches

Following the eight non potentiated twitches subjects underwent five potentiated twitches. Potentiated twitches involved the subject performing a maximal inspiratory pressure (MIP) maneuver, which involved a maximal inspiration against an occluded airway. The MIP was maintained for approximately five seconds and the subjects were provided with verbal encouragement to ensure a maximal effort. Subjects were stimulated once while performing the MIP and again once the MIP was completed. Subject were given the instructions, to put the MIP device in their mouth and to "suck" as hard as they could. Once the five second MIP was completed the subject was told to relax and "at the end of their next normal breath out to stick up your thumb", a stimulation was then given once the subject stuck up their thumb. After this stimulation subjects were given the instruction "on your next normal breath out stick it in your mouth and suck as hard as you can" then the subject would repeat the MIP and the stimulation protocol. This was repeated five times. Potentiated twitches were also monitored to ensure that twitches were initiated at FRC, using the same protocol as the non potentiated twitches. Both non potentiated twitches and potentiated twitches were used in the analysis of diaphragm fatigue however, it has been suggested that potentiated twitches detect diaphragm fatigue with greater sensitivity than non-potentiated twitches when the degree of fatigue is small (Laghi et al., 1995; Laghi et al., 1998).

The average amplitude of the twitch Pdi from the non-potentiated and potentiated twitches was used to establish baseline twitch Pdi and were used to detect diaphragm fatigue through comparison to post exercise twitch Pdi amplitude. Twitches were accepted based on criteria previously outlined (Laghi et al., 1996). Briefly, twitches were rejected from analysis if; 1) the twitch was not initiated at FRC; 2) there was any esophageal peristalsis in the breath immediately preceding the twitch; 3) the amplitude of the twitch was not within $\pm$ 10% of the other twitches done in that group of twitches and; 4) the Pes immediately preceding the twitch was $\pm$ 10% of the other twitches in the group.

Surface Electromyography

Electromyography (EMG) from the right and left side of the diaphragm was taken to ensure the diaphragm was supramaximally stimulated. The EMG electrodes are used to measure compound muscle action potentials (M-waves), which are a group of simultaneous action potentials from several muscle fibers in the same location. A plateau in M-wave amplitude with increasing phrenic nerve stimulation indicates that the diaphragm is being supramaximaly stimulated. As well, the M-waves from the EMG should not be altered from pre to post exercise, indicating that the same degree of electrical stimulation is still being delivered to the phrenic nerve. EMG electrodes were placed in the 7^{th} to 9^{th} intercostal space along the anterior axillary line. Different placements of the electrodes were tried on each subject until the largest and cleanest M-waves were obtained, as determined by the least degree of ECG superimposition, or the presence of electrical signal from the intercostal muscles.

EMG signals from both the right and left diaphragm were amplified and band-pass filtered (20 Hz – 2 kHz) to ensure that stimulation intensity remained supramaximal throughout the CMS protocol. The amplitudes of the M-waves were measured, from peak to trough, from the computer tracing. Individual M-waves were rejected when any of the following occurred: 1) A greater than 20% decrease in M-wave amplitude compared with the M-wave amplitudes that were obtained in the initial control period, 2) The twitch was not initiated near FRC as determined by the end-expiratory Poes (~ -5cmH_2O), 3) An inability to analyze the M-wave due to the superimposition of an ECG signal, 4) Oesophageal peristalsis occurred during or just before the initiation of the twitch, 5) There was a lack of diaphragmatic relaxation as demonstrated by diaphragmatic EMG activity and or an excess of Pga from baseline values before the twitch (Mador et al., 1996a).

In this study, however, large-stimulus artifact often obscured the M-waves making it difficult to obtain “clean” M-waves in several subjects. Furthermore, the electrodes often did not stay in place after the exercise as the subject had sweated, thus the amplitude of the M-waves, as a criterion for the acceptance of twitches cannot be reliably used. Discarding M-waves, as a criterion of twitch acceptance is not uncommon for reasons similar to those expressed in this study (Mador et al., 1996b and 2002).

Chest Wall Restriction

The techniques used in this study to perform chest wall restriction are similar to those previously documented (Miller et al., 2002). Maximum flow volume loops (MFVL) were generated

by each subject in the seated position prior to the application of the CWR straps until three reproducible measures of FVC were found. Maximum flow volume loops were later used in the analysis of operational lung volumes and expiratory flow limitation (EFL). The subject's chest wall and abdomen was then restricted using three to four inelastic straps, 4 and 6 inches wide. The number and size of the straps used varied based on the length and size of the subjects torso. The straps were fitted from the axillae to the hips, around the chest and abdomen. The straps were tightened manually while the subject exhaled to RV and secured using 11elcro. Pulmonary function testing was performed to determine if the desired degree of restriction (40% of FVC) had been achieved. If a 40% reduction in FVC was not been achieved than the straps were removed and reapplied.

Pressure Measurements

Oesophageal pressure and Pga were monitored using balloon tipped catheters (no. 47-9005, Ackrad Laboratory, Cranford NJ) placed in the oesophagus and stomach, respectively. Mouth pressure (Pm) was also measured at a port situated in the mouthpiece. Viscous Lidocaine (2%) was inserted into the nose and pharyngeal space to minimize the sensation during the placement of the catheters. The catheters were then inserted through the nose and down the oesophagus as the subject swallowed. The oesophageal catheter was placed ~45cm down from the nares, although the placement varied according to subject height and anatomy (Milic-Emili et al., 1964). The equation: 0.2666*the height of the subject; as per the manufacturers stipulation was used to approximate the location of the oesophageal balloon. Once the balloons were inserted the air was evacuated from the balloons by having the subject perform a valsalva maneuver, with the balloon open to the atmosphere. While the subject performed the valsalva maneuver a syringe was attached to the three-way stop cock blocking the balloon from the atmosphere. Pulling back on the syringe plunger until the syringe was in a non-vacuum position assured that the air had been evacuated from the balloon. One ml of air was then inserted into the oesophageal balloon and two ml of air were inserted into the gastric balloon. After insertion, both balloons were placed in the stomach of the subject, this was indicated by the presence of a positive deflection with a sniff. One of the balloons was then pulled out one cm at a time and the subject then performed a sniff. This was repeated until a negative deflection occurred in the Poes trace. Once a negative deflection occurred the balloon was pulled out an additional 10 cm. The validity of the placement of the oesophageal balloon was tested by having the subject exhale against an occluded airway and the placement was considered suitable if the

transpulmonary pressure (Ptp) remained constant while mouth pressure increased (Baydur et al., 1982). Transpulmonary pressure was calculated as the difference between the Poes and Pm. The position of the gastric catheter was determined by ensuring that the end-expiratory gastric pressure was positive while the subject was breathing at rest. The balloon tipped catheters and mouth pressure were attached to piezoelectric pressure transducers, which were calibrated across a range of pressures using a digital manometer (2021P, Digitron, Torquay England). All of the pressure signals were amplified, filtered (low-pass) at 50Hz, and digitized at 1000 Hz by a 16-bit analog-to-digital converter (200B, Direc Physiologic Recording System; Raytech Instruments) using the Direct/Win data acquisition software program (version 2.21, Raytech Instruments Inc).

Resting Data

Prior to the first exercise bout (without CWR) 10 minutes of resting data was obtained. The purpose of this data was to establish baseline values of Poes, Pga, Pdi, end tidal CO_2 ($PetCO_2$)and the ventilatory parameters, breathing frequency, V_T and V_E. Inspiratory capacity maneuvers were performed every two minutes during rest, which allowed for the determination of resting EELV and end inspiratory lung volume (EILV). Pressure-volume loops were also generated which allowed for the determination of the work of breathing at rest.

Steady State Exercise Test

All subjects performed 10 minutes of cycle exercise on an electronically braked cycle ergometer at an intensity of 45% of their peak power output as achieved in their maximal cycle test on first test day. The exercise tests were performed in both the control condition and experimental (CWR) condition, however, the order of the tests were not randomized. Subjects always underwent the control exercise condition first under the assumption that subjects would return to baseline levels of HR, $PetCO_2$, diaphragm contractility (Pdi twitch amplitude) and V_E after the control exercise relatively quickly and could then undergo the CWR exercise. During the steady state exercise tests, Pm, Poes, Pga, EFL, dynamic hyperinflation, duty cycle and ventilatory parameters V_E, VT, breathing frequency, and $PetCO_2$ were monitored and recorded.

Operational Lung Volumes and Expiratory Flow Limitation

In order to assess changes in EELV and EILV, IC maneuvers were performed at rest and every two minutes during exercise. Subjects were prompted to perform the IC maneuvers with the instruction "at the end of a normal breath out take a maximal breath in as hard and as fast as you can." Subjects were given ample practice at rest and during exercise on the familiarization day in performing Ics to ensure reproducibility. Inspiratory capacity maneuvers were completed every two minutes during rest and in both exercise bouts. Ics were considered acceptable in the unrestricted exercise condition if the peak inspiratory Poes matched that of the peak inspiratory Poes obtained at rest. In the CWR exercise Ics were considered acceptable if the peak inspiratory Poes was within $\pm$ 10% of the other Ics performed during the CWR exercise bout. Ics were analyzed by examining 6 breaths prior to the IC to monitor and correct for drift in the volume signal as well as to monitor any change in breathing pattern prior to the IC.

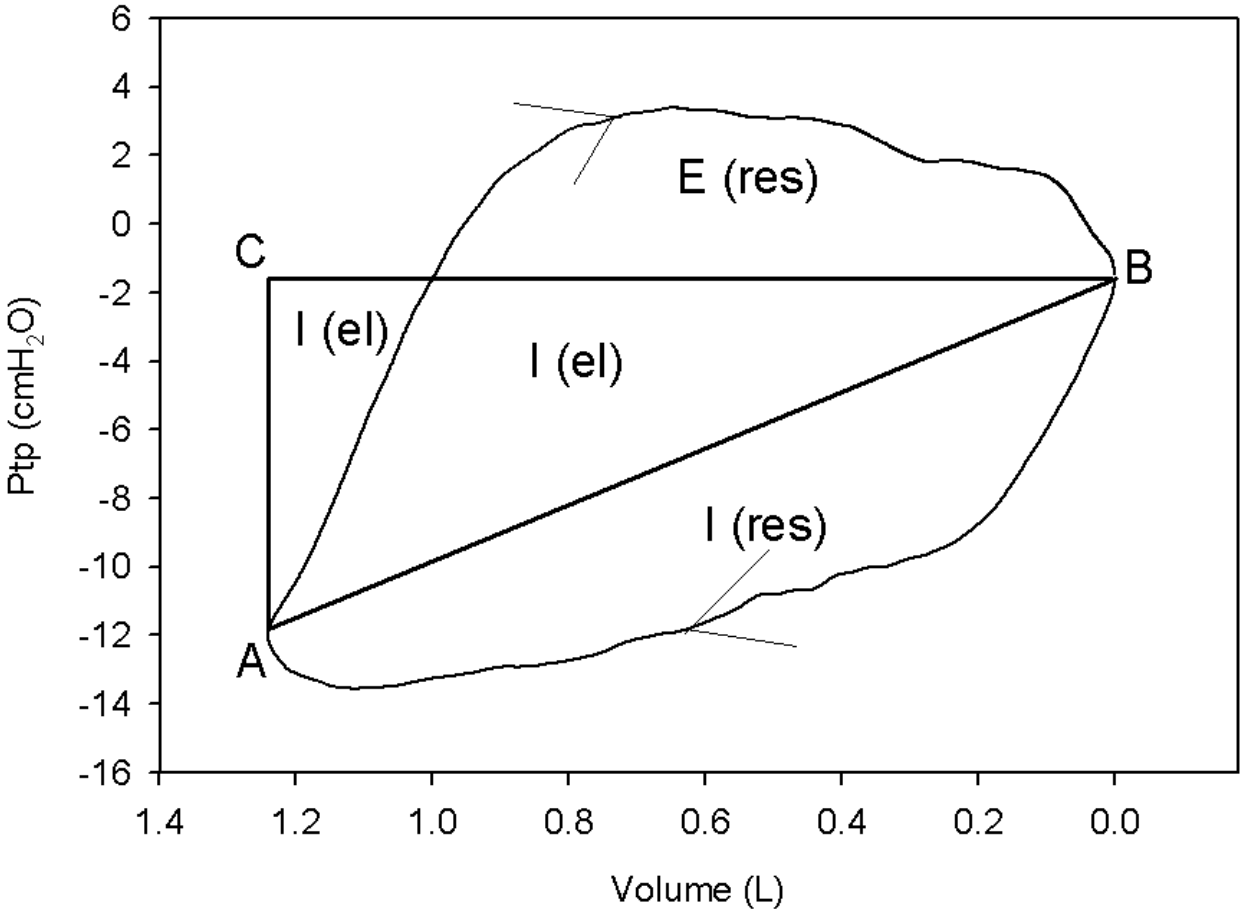
End-expiratory lung volume was calculated by subtracting the subjects IC from their resting FVC with the assumption that the total lung capacity remains constant during exercise (Johnson et al. 1999). End-inspiratory lung volume (EILV) was calculated by adding the EELV to the V_T. Measuring EELV with this method allowed for the placement of tidal flow volume loops obtained during rest and exercise inside the subject's MFVL. Breathing patterns at rest and during exercise and the presence and degree of EFL was then analyzed (Miller et al. 2002). Expiratory flow limitation was considered present if there was an overlap between the subjects MFVL and the tidal flow volume loops (Mota et al., 1999, Valta et al., 1994). Breathing patterns were analyzed by examining where the subjects were breathing inside their MFVL. Dynamic hyperinflation was considered evident if the subject increased their EELV near the end of exercise to breath at volumes greater than FRC and flow rates.

Work of Breathing

The work of breathing was assessed by integrating the area under the transpulmonary pressure (Ptp)-volume curve. Transpulmonary pressure is the difference between Pm and Poes. Oesophageal pressure is used as an indication of pleural pressure and Pm is an indication of airway pressure. Both Ptp and Poes can be used to create pressure-volume curves for the purposes of calculating the work of breathing as both Poes and Ptp are pressures associated with the expansion of the lungs (Babcock et al., 2002; Benditt 2005; Miller et al., 2002). Using the Poes to calculate the work of breathing

results in slightly larger values as it does not account for airway pressure. In this study the Poes-volume curve was used to determine the work of breathing, instead of Ptp, for some subjects as Pm was not obtained during exercise. The pressure and volume from several breaths during exercise was averaged and a customized software program (LabVIEW software V6.1, National Instruments) was used to integrate the area under the average transpulmonary pressure-volume curve (Otis, 1964). The pressure-volume loop was divided into three distinct components: flow resistive work done on inspiration (I(res)), elastic work done on inspiration (I(el)) and total work done on expiration (E(tot)). Using this method the resistive work on expiration is determined and the elastic work on expiration cannot be determined using this method. As seen in figure 1, inspiration occurs along the curve from B to A. In order for this change in volume to occur the pressure change from C to A must be generated. The area inside the triangle BCA is the elastic work done on inspiration while the area indicated by the I(res) is the flow resistive work on inspiration and the area E(tot) is the total work done on expiration. The total work of breathing is the sum of these three areas. If the small triangle contained outside the pressure-volume loop was not included in the total for the work of breathing than it would be underestimated. The work of breathing determined using this method was then multiplied by the breathing frequency to quantify the amount of work done per minute by the respiratory system. This method for analyzing the work of breathing is similar to methods was originally described by (Otis 1964, Milic-Emili et al., 1962).

Figure 1. Transpulmonary pressure-volume loop generated during CWR exercise. The total work of breathing is the area inside the entire figure, including the area of the triangle with side AC, outside the loop. The work of breathing is broken down into its constituent components, which are denoted by the following abbreviations. Definitions of abbreviations; I(res) = flow resistive work done on inspiration, E(tot) = flow resistive work done on expiration, I(el) = elastic work done on inspiration.



STATISTICAL ANALYSIS

The Pdi twitch amplitude from the CWR and control conditions were compared for the presence of diaphragm fatigue. One way repeated measures ANOVA procedures were completed to examine possible differences between baseline Pdi twitch values and post exercise Pdi twitch values. Significant F-ratios were further examined using t-tests with Bonferonni adjustments. As well, 2X5 repeated measures ANOVAs were done to compare the effect of condition (2) across time (5) during exercise on the recorded ventilatory parameters, duty cycle, inspiratory pressures, RPEs, SaO_2 and HR. Significant F-ratios were further examined using t-tests with a Bonferonni adjustment. T-tests

were done for the eighth and tenth minute of exercise to avoid doing an unnecessary number of t-tests when the primary interest in exercise variables was at end stage exercise. Looking for differences in the end stages of exercise also allows for comparisons with other CWR studies which only reported measures taken at end stage exercise (Miller et al., 2000). T-tests were also performed to compare descriptive statistics between the CWR condition and the control condition. A linear Pearson product moment correlational analysis was also done to examine the relationship between the percent drop in Pdi from baseline and the elastic work of breathing done on inspiration, at ten minutes post CWR exercise. The alpha level was set at $p < 0.05$ for all statistical comparisons.

RESULTS

Subject Characteristics and Resting Pulmonary Function

Eight subjects volunteered to participate in this study but one was excluded on the basis of inconsistent Pdi twitch data, due to faulty balloon placement. Descriptive and anthropometric data for all subjects is shown in table 1. All subjects were healthy males between the ages of 21 and 39 and were within the normal range for BMI. Table 2 shows resting pulmonary function data and the percent predicted values for each of the measure. Subject 7 had an FVC of 6.58 L and an FEV_1 of 4.72 L, therefore this subject had an $FEV_{1.0}$/FVC of 71.7%. However, this subject was included in the analysis despite this low $FEV_{1.0}$/FVC because he was still able to expel more than 4.5 L of air in one second and because the shape of his MFVL was normal. Furthermore, subject 7 had no history of asthma or any other obstructive disorder.

Table 1. Descriptive and anthropometric data. Values given are for individual subjects as well as group means and standard deviation. Definitions of abbreviations; BMI = body mass index

	Age	Height (cm)	Weight (kg)	BMI (kg/m^2)
S1	39	174.0	71.1	23.5
S2	27	184.5	84.0	24.7
S3	26	170.0	65.6	22.7
S4	21	171.0	64.8	22.2
S5	31	183.0	83.4	24.9
S6	39	169.5	69.1	24.1
S7	27	177.0	85.6	27.3
Mean	30	175.6	74.8	24.2
SD	6.8	6.2	9.2	1.7

Table 2. Resting pulmonary function data for individual subjects, as well as, group means and standard deviations. Definitions of abbreviations; FVC = forced vital capacity; $FEV_{1.0}$ = forced expiratory volume in one second; $FEV_{1.0}$/FVC = forced expiratory volume in one second over forced vital capacity; PEF = peak expiratory flow rate; MVV = maximum voluntary ventilation; %pred = percent predicted.

	S1	S2	S3	S4	S5	S6	S7	Mean	SD
FVC (L)	4.66	6.44	4.11	6.32	5.33	4.26	6.58	5.39	1.07
FVC (%pred)	100	116	86	127	99	97	128	108	16
$FEV_{1.0}$ (L)	3.72	5.17	3.35	5.16	4.37	3.74	4.72	4.32	0.73
$FEV_{1.0}$ (%pred)	96	111	82	121	98	102	110	103	13
$FEV_{1.0}$/FVC (%)	79.8	80.3	81.5	81.6	82	87.8	71.7	80.7	4.8
$FEV_{1.0}$/FVC (%pred)	100	97	99	98	100	109	87	99	6
PEF (L/sec)	9.5	12.7	9.3	11.2	10.8	12.8	9.7	10.8	1.5
PEF (%pred)	103	123	98	115	107	144	98	113	17
MVV (L/min)	175.7	202.7	174.5	207.9	202.4	202	200.8	195.1	13.9
MVV (%pred)	128	127	122	140	131	153	134	134	10

Resting Ventilatory Data

Resting ventilatory and duty cycle data from the final two minutes of the resting period before the unrestricted exercise bout were averaged and are displayed in table 3. $PetCO_2$ could only be obtained for three of the subjects. EELV and EILV could not be obtained for two subjects due to their inability to perform inspiratory capacity maneuvers. It is evident from the breathing frequencies and V_T present in this group of subjects that there is some degree of hyperventilation occurring during rest.

Table 3. Resting ventilatory data. Values were collected during the final two minutes of the ten minute rest period prior to unrestricted exercise. Definitions of abbreviations; $PetCO_2$ = partial pressure of end tidal CO_2; V_T = tidal volume; F_b = breathing frequency; V_E = minute ventilation; T_I = inspiratory time; T_E = expiratory time; T_{TOT} = total respiratory time; T_I/T_{TOT} = inspiration time/total time; EELV = end expiratory lung volume; EILV = end inspiratory lung volume.

	S1	S2	S3	S4	S5	S6	S7	Mean	SD
$PetCO_2$ (mmHg)	41.5		45.1		35.4			40.6	4.9
V_T (L)	0.8	1.0	0.9	1.4	0.8	0.6	1.7	1.0	0.4
F_b (breaths/min)	13.4	17.0	8.6	10.1	16.8	17.5	11.3	13.6	3.6
V_E (L/min)	10.5	17.0	7.8	14.6	12.9	9.8	19.7	13.2	4.2
T_I (sec)	1.6	1.4	2.7	1.4	1.3	0.9	6.1	2.2	1.8
T_E (sec)	2.6	1.8	5.9	2.0	1.8	2.8	1.8	2.7	1.5
T_{TOT} (sec)	4.2	3.2	8.6	3.38	3.1	3.7	7.9	4.9	2.4
T_I/T_{TOT}	0.4	0.4	0.3	0.4	0.4	0.2	0.8	0.4	0.2
EELV (L)	2.5		1.5	3.1	2.3	2.4		2.6	0.8
EILV (L)	3.3		2.5	4.6	3.2	3.0		3.6	1.1

Peak Exercise Data

Metabolic, ventilatory and performance data obtained at peak exercise (final 30 seconds) are displayed in table 4. All subjects reached respiratory exchange ratios of greater than 1.1, indicating that they likely achieved a true maximal effort. Although volitional fatigue did occur in all subjects, RPE values reported were variable. The exercised tests lasted on average 690 $\pm$ 84 seconds and the mean maximal power output achieved was 345 $\pm$ 42 Watts. Ventilation rates were 149 $\pm$ 27 L on average and 76 $\pm$ 12% of the mean MVV. Subjects were relatively fit with the mean relative VO_{2MAX} being 50.3 $\pm$ 9.3 ml/kg/min. The lowest VO_{2MAX} achieved was 31.1 ml/kg/mim, however, this subject only reached a ventilatory rate of 98.7L which was only 48.8% of his MVV, nonetheless he did attained his age-predicted maximum heart rate.

Table 4. Peak exercise values during the incremental cycle test to exhaustion on Day 1 of testing. Individual subject data, as well, as group means and standard deviations. Definitions of abbreviations; VO_2 = Oxygen consumption; VCO_2 = production of carbon dioxide; RER = respiratory exchange ratio; Fb = breathing frequency; V_T = tidal volume; V_E; ventilation; V_E/VO_2 = ventilatory equivalent for oxygen; V_E/VCO_2 = ventilatory equivalent for carbon dioxide; V_E/MVV = minute ventilation / maximum voluntary ventilation; HR = heart rate; RPE = rating of perceived exertion; SaO_2 = oxygen saturation from pulse oximetry.

	S1	S2	S3	S4	S5	S6	S7	MEAN	SD
VO_2 (ml/kg/min)	58.7	58.0	57.5	54.3	45.2	31.1	47.4	50.3	9.3
VO_2 (L/min)	4.2	4.9	3.8	3.5	3.8	2.2	4.1	3.8	0.8
RER	1.1	1.2	1.2	1.2	1.2	1.3	1.2	1.2	0.1
Fb (breaths/min)	56.1	46.5	55.8	54.2	72.1	43.6	51.6	54.3	8.5
V_T (L)	2.4	3.1	2.1	3.2	2.4	2.1	3.1	2.6	0.5
V_E (L/min)	143.5	169.3	127.9	173.7	184.0	98.7	145.9	149.0	27.4
V_E/VO_2	34.5	34.6	33.9	49.3	48.8	46.0	35.9	40.4	6.7
V_E/VCO_2	32.1	29.2	28.2	40.2	40.4	34.6	30.1	33.5	4.7
V_E/MVV (%)	81.7	83.5	73.3	83.5	90.9	48.8	72.7	76.4	12.7
HR (bpm)	173.0	185.0	183.0	198.0	184.0	191.0	180.0	184.9	7.4
Exercise Duration (sec)	760	780	614	680	744	528	726	690	84
Peak Power (W)	380	390	307	340	372	264	363	345	42
45% Peak Power (W)	171	176	138	153	167	119	163	155	20
Dyspnea (Borg)	7	8	10	8	10	7	7	8.1	1.3
Leg Discomfort (Borg)	9	8	9	9	10	9	5	8.4	1.6
SaO_2 (%)	93	95	97	99	94	95	97	95.7	2.1

Chest Wall Restriction Data

Data on the degree of restriction for each subject as well as the group mean and standard deviation are displayed in table 5. Subject 3 and 4 were slightly less than 40% restricted while all other subjects were more modestly greater than 40% restricted. The greatest degree of restriction achieved was in subject 6 with a 47.4% restriction. The least amount of restriction achieved was in subject 3 at 31.5% restriction. The group mean FVC in the CWR condition was significantly less than the group mean in the NCWR condition (3.1 ± 0.6 L vs. 5.3 ± 1.0 L, $p < 0.01$) and the average restriction for the group was 40.8 ± 5.09%. The goal of 40% restriction was achieved in five of seven subjects. The minor variation in the degree of restriction across subjects is due to two subjects, one who was only 31.5% restricted and one who was 47.4% restricted. In the subject who was only 31.5% restricted the degree of restriction may have been related to his small unrestricted FVC, on the

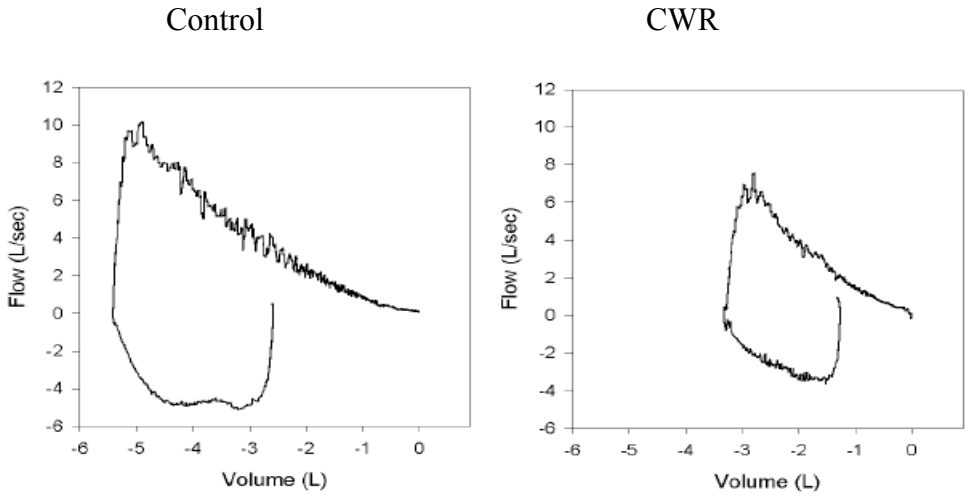
experimental test day the experimenter could not get the CWR straps tight enough to produce a higher degree of restriction. In the subject who was 47.4% restricted, a higher degree of restriction than was necessary was achieved but the experimenter continued the experiment with that subject despite this.

The degree of restriction is also shown for an individual subject in figure 2 which depicts the MFVL for both conditions. The size of the entire loop is significantly smaller and that much lower peak expiratory flow rates were achieved.

Table 5. Forced Vital Capacity with and without CWR. Individual data, as well as group means and standard deviations. Definitions of abbreviations: FVC = Forced Vital Capacity; % Restriction = the percent reduction in FVC in CWR from NCWR; * significantly different from unrestricted forced vital capacity ($p < 0.01$).

	FVC NCWR	FVC CWR	% RESTRICTION
1	4.9	2.9	41.0
2	6.5	3.5	45.4
3	4.0	2.8	31.5
4	6.2	3.8	38.9
5	5.4	3.2	40.9
6	4.1	2.2	47.4
7	6.1	3.6	40.6
Mean	5.3	3.1*	40.8
SD	1.0	0.6	5.1

Figure 2. Maximal Flow Volume Loops for one subject in the control condition (left) and CWR condition (right). The CWR MFVL shows the significantly reduced forced vital capacity and peak expiratory flow rate.



Steady State Exercise Data

Both steady state exercise bouts were 10 minutes long and at 45% of the peak power output achieved in the maximal aerobic test on the first testing day (see table 4). Group mean values for ventilatory data, heart rate, SaO_2, $PetCO_2$ and duty cycle during the steady state exercise in both the control and CWR conditions are shown in Table 6.

Heart rate was significantly higher in the CWR condition compared to the unrestricted condition in the eighth and tenth minute (148 $\pm$ 16 bpm vs. 134 $\pm$ 20 bpm and 151 $\pm$ 16 bpm vs. 136 $\pm$ 20, bpm $p < 0.01$) and SaO_2 was significantly lower at these time points (93 $\pm$ 3% vs. 96 $\pm$ 1% and 94 $\pm$ 3 vs. 96 $\pm$ 1, $p < 0.05$). The breathing frequency was significantly higher in the CWR condition at the eighth and tenth minute (40.5 $\pm$ 7.4 bpm vs. 25.5.5 $\pm$ 4.5 bpm and 43.1 $\pm$ 7.9 bpm vs. 26.3 $\pm$ 5.2 bpm $p < 0.01$) compared to the unrestricted condition, while the V_T was significantly lower (1.7 + 0.3L vs. 2.4 + 0.6 L and 1.6 + 0.3 L vs. 2.3 + 0.6 L, $p < 0.01$) in the CWR condition at these same time points. Despite the differences in breathing pattern between the two conditions there was no difference in V_E. Individual data for breathing frequency, V_T and V_E for both conditions is displayed in figure 3.

All of the components of duty cycle were significantly different between the two conditions (see Table 6). Inspiratory time, expiratory and total respiratory time, were all significantly lower in the CWR condition compared to the control condition at the eighth and tenth minute. This corresponds to the increased breathing frequency seen in the CWR condition. Despite these differences in the components of duty cycle there was no difference in duty cycle between the two groups.

The dyspnea ratings were significantly higher for the CWR condition compared to the control condition in both the 8^{th} and 10^{th} minute of exercise (5.5 $\pm$ 1.6 RPE vs. 1.6 $\pm$ 1.0 RPE and 5.8 $\pm$ 1.3 RPE vs. 2.6 $\pm$ 0.9 RPE, $p < 0.01$) and were approaching those seen in the final moments of the maximal aerobic test (see Table 6). This indicates that the level of breathing discomfort was near maximal despite the relatively low exercise intensity of 45% of VO_{2MAX}. There was no difference in the ratings of perceived exertion (RPE) for leg discomfort between the control and CWR exercise conditions, however, the RPE for leg discomfort did increase significantly over time in both groups (see Table 6). Ratings of perceived exertion for both the conditions, CWR vs. the control and for leg discomfort and dyspnea are seen in figure 4.

Table 6. Steady state exercise data for the control (top) and CWR (bottom) groups. Numbers reported every two minutes across the 10 minutes of exercise are group means and standard deviations. Definitions of abbreviations. HR = Heart rate; V_T = tidal volume; Bf = breathing frequency; = V_E = minute ventilation; $PetCO_2$ = end tidal CO_2; SaO_2 = oxygen saturation; T_I = inspiratory time; T_E = expiratory time; T_{TOT} = total respiratory time; T_I/T_{TOT} = inspiratory time/total respiratory time, * = statistically significantly different from the control condition ($p < 0.05$).

	Control				
	2 Minutes	4 Minutes	6 Minutes	8 Minutes	10 Minutes
HR (bpm)	124 ± 18	126 ± 20	132 ± 21	134 ± 20	136 ± 20
Percent of Max HR (%)	67.2 ± 7.8	68.2 ± 8.8	71.5 ± 9.6	72.4 ± 8.9	74.0 ± 9.0
V_T (L)	2.3 ± 0.8	2.7 ± 0.7	2.7 ± 0.8	2.4 ± 0.6	2.3 ± 0.6
Bf (bpm)	20.9 ± 5.7	22.7 ± 5.5	22.4 ± 6.6	25.5 ± 4.5	26.3 ± 5.2
V_E (L/min)	45 ± 11	58 ± 12	56 ± 12	60 ± 10	59 ± 11
$PetCO_2$ (mmHg)	46.7 ± 4.9	46.0 ± 3.9	45.8 ± 3.7	45.2 ± 3.7	44.2 ± 4.7
SaO_2 (%)	97 ± 1.3	97 ± 0.5	97 ± 0.7	96 ± 1	96 ± 1
Dyspnea (Borg)	1.7 ± 1.1	2.1 ± 1.2	2.6 ± 1.0	1.6 ± 1.0	2.6 ± 0.9
Leg Discomfort (Borg)	2.3 ± 0.9	2.6 ± 1.0	2.8 ± 0.9	2.8 ± 0.9	2.8 ± 0.9
T_I (sec)	1.54 ± 0.67	1.29 ± 0.42	1.29 ± 0.46	1.10 ± 0.27	1.06 ± 0.25
T_E (sec)	1.65 ± 0.38	1.43 ± 0.31	1.42 ± 0.36	1.29 ± 0.43	1.23 ± 0.30
T_{TOT}	3.19 ± 1.02	2.72 ± 0.69	2.71 ± 0.79	2.40 ± 0.43	2.30 ± 0.48
T_I/T_{TOT}	0.47 ± 0.05	0.47 ± 0.05	0.47 ± 0.05	0.46 ± 0.06	0.46 ± 0.05
V_T/T_I (L/sec)	1.4 ± 0.8	2.1 ± 0.3	2.1 ± 0.3	2.2 ± 0.2	2.2 ± 0.3

	CWR				
	2 Minutes	4 Minutes	6 Minutes	8 Minutes	10 Minutes
HR (bpm)	133 ± 15	136 ± 16	143 ± 17	148 ± 16*	151 ± 16*
Percent of Max HR (%)	72.7 ± 6.9	74.9 ± 7.8	78.1 ± 8.6	81.0 ± 8.5	82.6 ± 8.2
V_T (L)	1.6 ± 0.3	1.7 ± 0.2	1.6 ± 0.2	1.7 ± 0.3*	1.6 ± 0.3*
Bf (bpm)	32.7 ± 10.7	37.2 ± 8.7	39.4 ± 7.4	40.5 ± 7.4*	43.1 ± 7.9*
V_E (L/min)	52 ± 16	61 ± 11	62 ± 8	66 ± 9	67 ± 8
$PetCO_2$ (mmHg)	43.4 ± 4.7	44.2 ± 4.3	43.7 ± 3.2	43.8 ± 3.4	42.9 ± 3.4
SaO_2 (%)	94 ± 2.6	95 ± 2	93 ± 3	93 ± 3*	94 ± 3*
Dyspnea (Borg)	4.1 ± 1.5	4.8 ± 1.5	5.1 ± 1.6	5.5 ± 1.6*	5.8 ± 1.3*
Leg Discomfort (Borg)	2.1 ± 0.8	2.3 ± 0.7	2.4 ± 0.9	2.6 ± 1.3	2.7 ± 1.4
T_I (sec)	0.89 ± 0.23	0.81 ± 0.22	0.77 ± 0.18	0.73 ± 0.17*	0.71 ± 0.15*
T_E (sec)	0.89 ± 0.23	0.81 ± 0.15	0.80 ± 0.18	0.73 ± 0.13*	0.73 ± 0.17*
T_{TOT}	1.78 ± 0.39	1.61 ± 0.35	1.56 ± 0.31	1.47 ± 0.29*	1.44 ± 0.43*
T_I/T_{TOT}	0.50 ± 0.06	0.50 ± 0.04	0.49 ± 0.05	0.5 ± 0.03	0.50 ± 0.05
V_T/T_I (L/sec)	1.9 ± 0.3	2.2 ± 0.2	2.2 ± 0.2	2.3 ± 0.3	2.3 ± 0.3

Figure 3. Individual data for tidal volume, breathing frequency and minute ventilation for the control condition (left) and the CWR conditions (right). Definitions of abbreviations, V_T = tid al volume; V_E = minute ventilation.

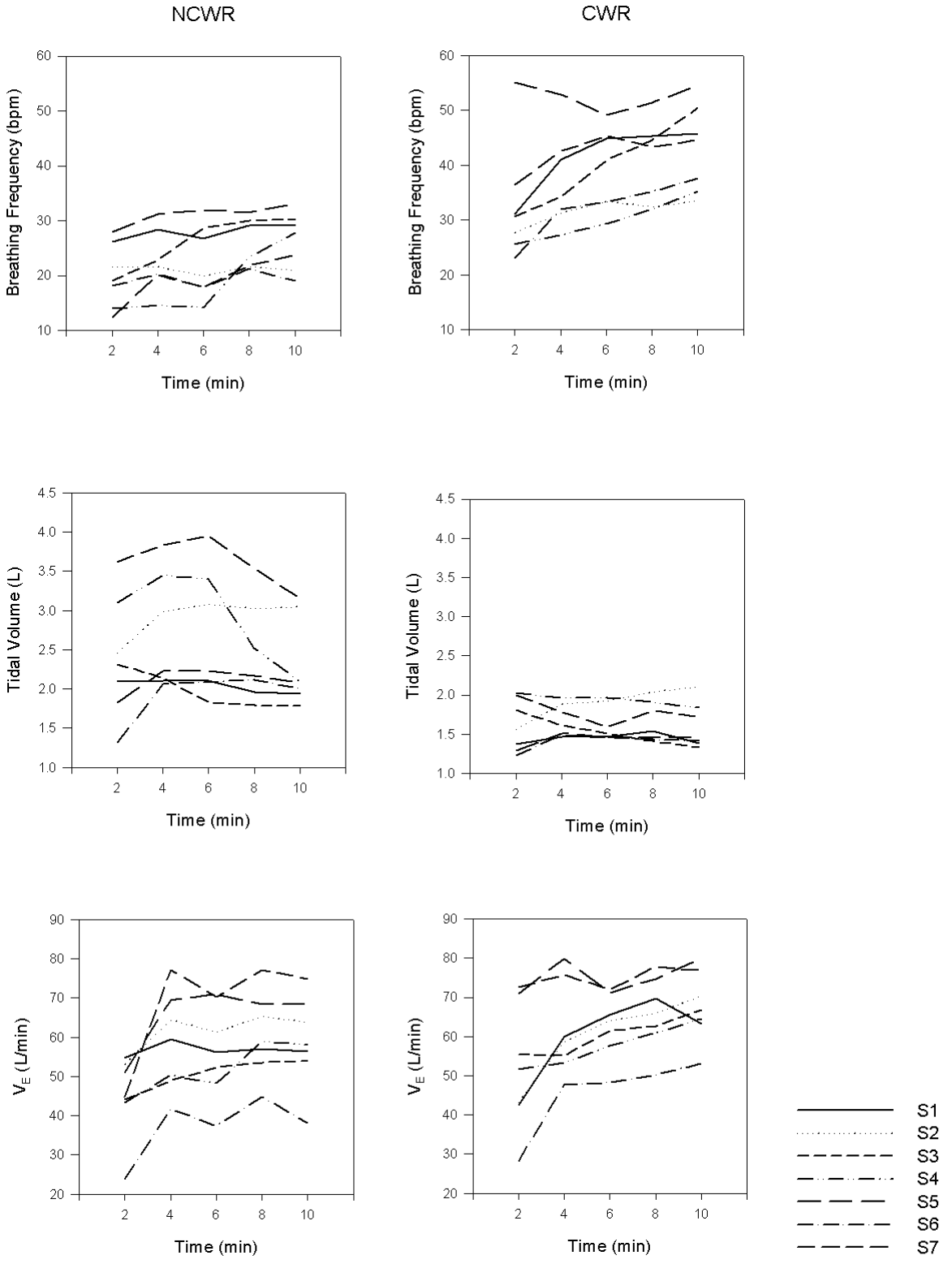
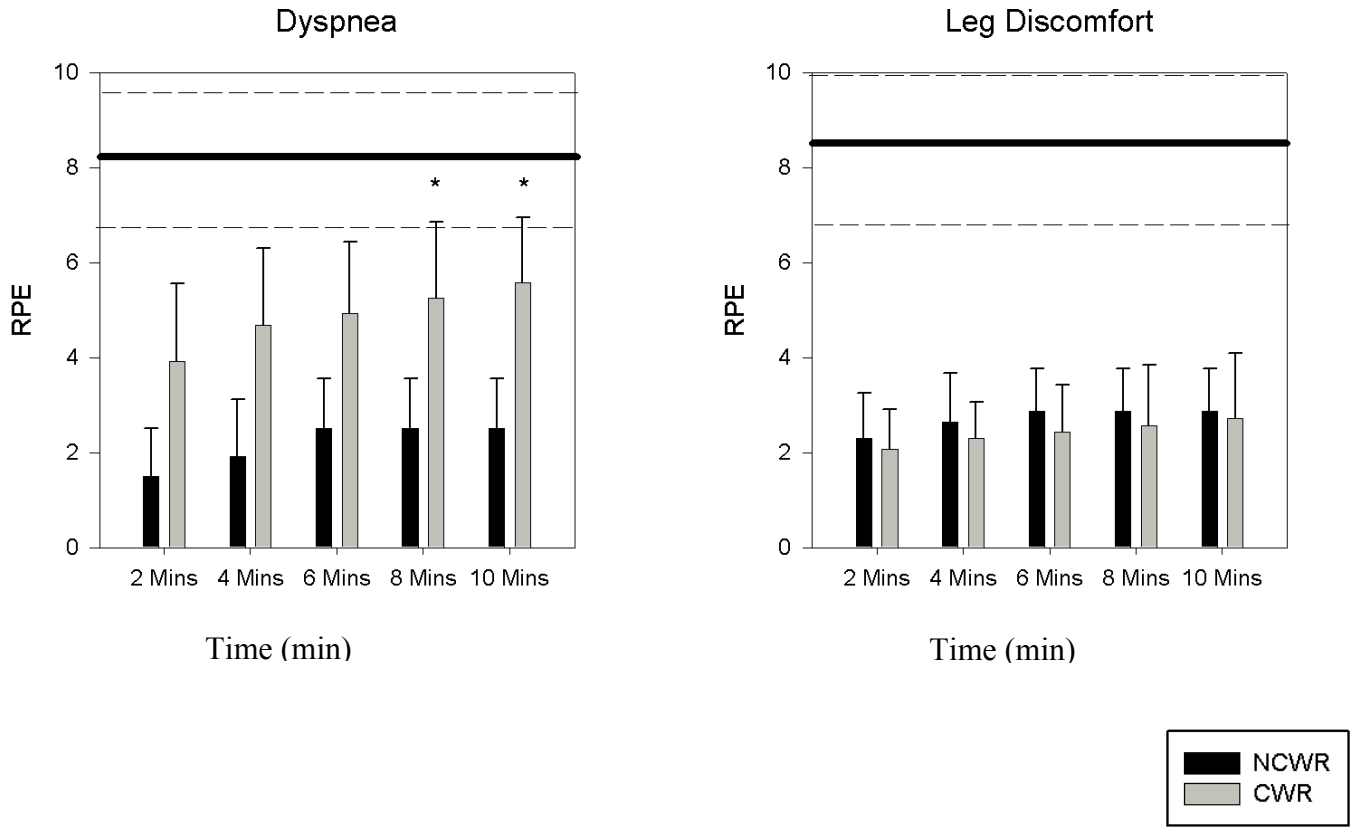


Figure 4. Ratings of perceived exertion for dyspnea (left) and leg discomfort (right) for the control condition and the chest wall restriction condition. Bars indicate group means and error bars are standard deviation. Vertical grey bars represent chest wall restriction and vertical black bars represent the control condition. Data is given for five time points during the sub-maximal steady state exercise at 2, 4, 6, 8 and 10 minutes. The solid black horizontal line across both figures represents the mean rating of perceived exertion for either legs or breathing from the final measurement during the maximal aerobic test. The two dashed lines represent the standard deviations for the mean taken at max. Definition of abbreviations; RPE = rating of perceived exertion, * = means are statistically significantly different from the control condition ($p < 0.01$).



Lung Volumes During Steady State Exercise

Restriction of the chest wall resulted in significantly reduced forced vital capacities in all subjects. This is shown for an individual subject in figure 3 and as group mean data in table 5. The reduction in FVC resulted in a reduced FRC forcing subjects to breath at lower lung volumes. This is represented as a significant reduction in the EELV in the CWR exercise condition compared to the control condition in the eighth and tenth minutes of exercise (1.1 ± 0.5L vs. 2.4 ± 0.7 L and 1.1 ± 0.5L vs. 2.5 ± 0.7L, $p < 0.01$) and is shown in figure 5. When the EELV was examined as a percentage of FVC it is significantly lower in the CWR condition compared to the control condition

at the eighth and tenth minutes (29.3 ± 8.1% vs. 41.7 ± 9.0% and 31.2 ± 8.0% vs. 42.9 ± 8.6%, $p < 0.05$). This indicates that the subjects are utilizing a greater proportion of their expiratory reserve volume (ERV). End expiratory lung volume as a percentage of FVC is shown in figure 6.

Subjects also had significantly reduced EILV in the CWR compared to the control condition (2.8 ± 0.5 L vs. 4.6 ± 0.9 L and 2.8 ± 0.5 L vs. 4.5 ± 0.9 L, $p < 0.01$) due to the reduction in FVC. The reduced FVC also resulted in a reduction in inspiratory reserve volume, which ultimately increased the ratio of V_T/IRV. However, when EILV is expressed as a percentage of FVC the two conditions are statistically significantly different. Figure 6 shows EELV and EILV as a percentage of FVC across the five time points during exercise.

Figure 5. Absolute volumes for end expiratory lung volume and end inspiratory lung volume in both the control (left figure) and chest wall restricted (right figure) conditions during exercise. Points indicate group means and error bars indicate standard deviation. Solid circles represent end expiratory lung volume and open circles represent end inspiratory lung volume. End expiratory and end inspiratory lung volume were significantly less in the 8th and 10th minute of the chest wall restricted exercise compared to the control exercise. Definition of abbreviations; NCWR = no chest wall restriction; CWR = chest wall restriction.

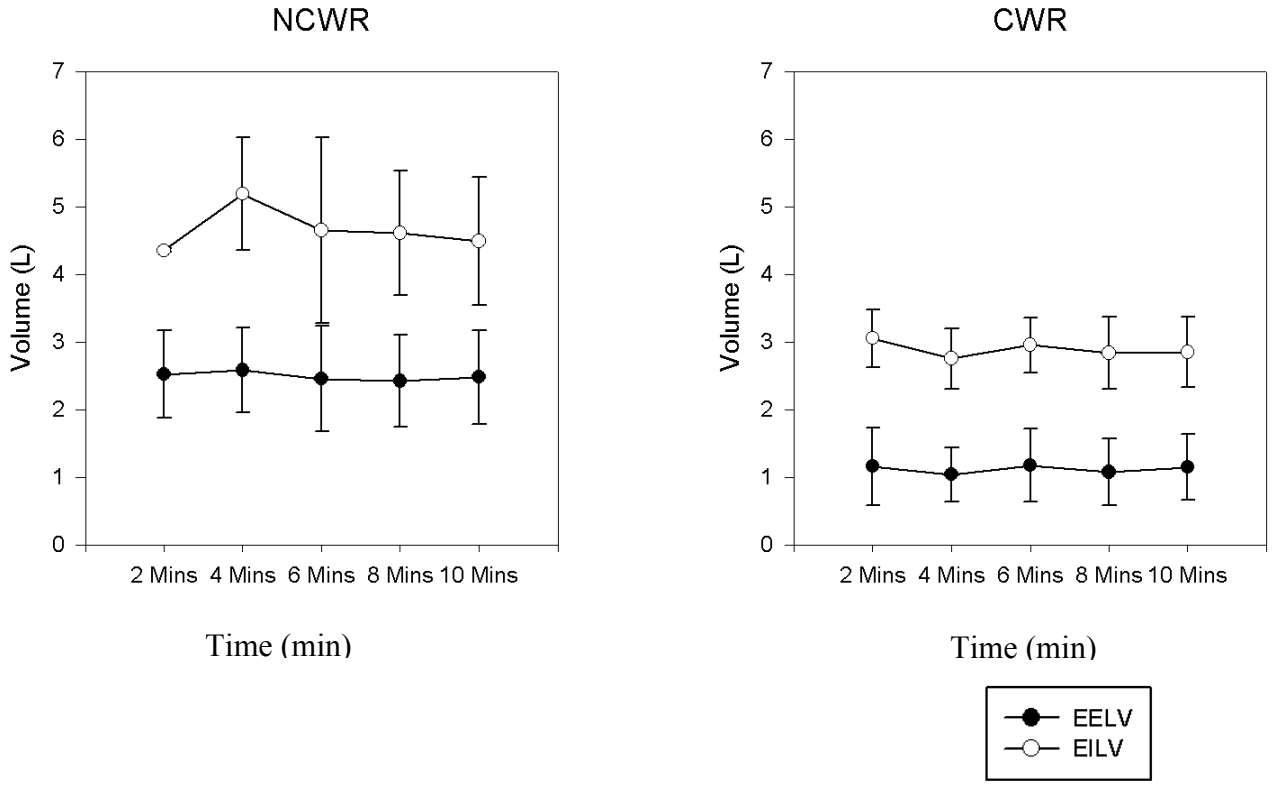
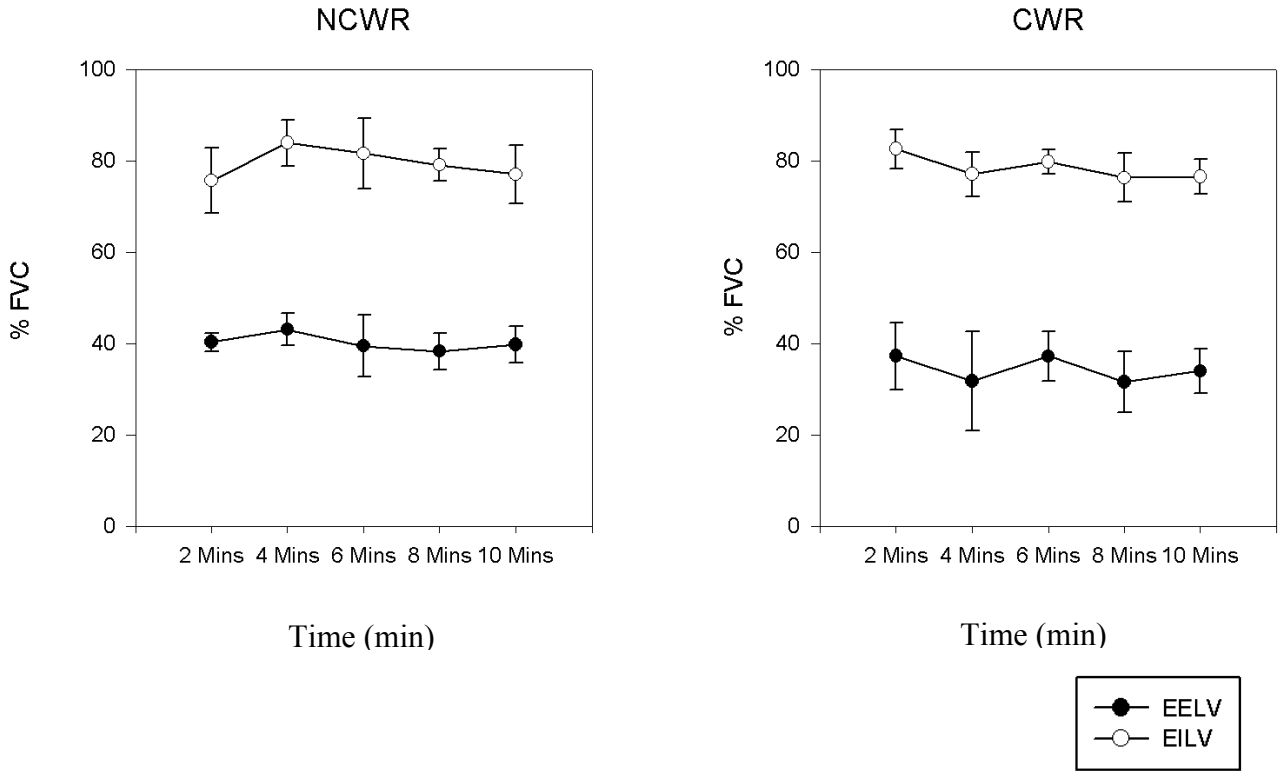


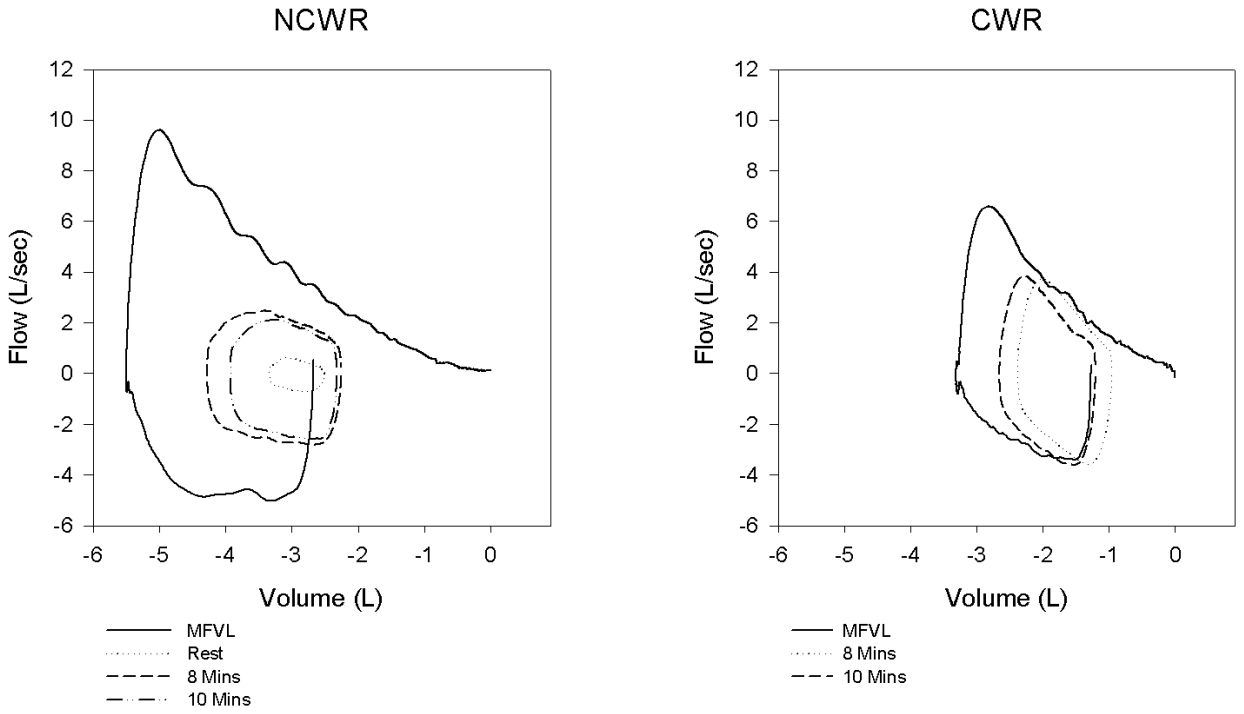
Figure 6. End expiratory lung volume and end inspiratory lung volume as a percentage of forced vital capacity for both the control condition (left figure) and the chest wall restricted condition (right figure) across exercise. Points indicate group means and error bars indicate standard deviation. Solid circles represent end expiratory lung volume and open circles represent end inspiratory lung volume.



The change in lung volumes and breathing patterns can also be shown when tidal breaths are plotted inside the MFVLs for each subject and for condition. Tidal breaths at rest and during exercise in both conditions are plotted inside the MFVLs for one subject in Figure 7 (MFVLs and tidal breaths during exercise for other subjects are in shown in appendix B, Figure 17). The change in lung volumes between the conditions is evident as the size of the MFVL is drastically reduced and the tidal breaths during exercise take up a much more significant portion of the MFVL in the CWR condition versus the control condition. In the control condition the tidal breaths do not approach the boundaries of the MFVL and the subject has significant area to increase both flow and volume. However, in the CWR condition the tidal breaths during exercise are approaching the boundaries of the MFVL and the subject experiences flow limitation at the eighth minute mark of exercise. All subjects without exception showed EFL in the CWR condition (see appendix B, Figure 17). In the representative subject shown here and in some of the other subjects, the breathing pattern changed

after the subject experienced flow limitation and consequently they increased their EELV to access higher flow rates. This is seen as the tidal loop for the tenth minute in the CWR exercise has shifted to the left increasing EELV but reducing EFL.

Figure 7. Maximal flow volume loops and tidal breaths at rest (control condition only) and at the eight and tenth minute during exercise in both the control (left figure) and chest wall restricted (right figure) conditions from one subject. The figure shows the change in absolute lung volumes as seen in the significant reduction in FVC in the CWR condition compared to the control condition resulting in a significantly reduced inspiratory reserve volume. The figure also shows the reduction in peak expiratory flow in the chest wall restricted condition compared to the control condition and the resulting expiratory flow limitation, which occurs in the chest wall restricted condition in the eighth minute and is depicted by the tidal breath overlapping with the maximal flow volume loop. End expiratory lung volume and end inspiratory lung volume are both significantly reduced in the chest wall restricted condition but in the tenth minute there is a leftward shift in the tidal breaths resulting in an increase in the operational lung volumes. This results in dynamic hyperinflation and an increase in the functional residual capacity at the end of the exercise bout. Definitions of abbreviations; MFVL = maximal flow volume loop.



Oesophageal and Transdiaphragmatic Pressure-Time Integrals

Oesophageal and transdiaphragmatic pressure were monitored during control and CWR exercise and time integrals for Poes ($\int$Poes**f*) and Pdi ($\int$Pdi**f*) were calculated. Group means and standard deviations for $\int$Poes**f* and $\int$Pdi**f* during exercise are displayed in table 7. There was no difference between the groups for $\int$Poes**f* at any of the time points. Transdiaphragmatic pressure time integral was statistically significantly greater in the eighth and tenth minute in the CWR exercise compared to the control exercise (863 $\pm$ 401cmH_2O**f* vs. 265 $\pm$ 62 cmH_2O**f* and 961 $\pm$ 342 cmH_2O**f* vs. 272 $\pm$ 96 cmH_2O**f*, $p < 0.01$)

Table 7. Oesophageal and transdiaphragmatic pressure time integrals during control and CWR exercise. Values are group means and standard deviations. Definitions of abbreviations, $\int$Pes**f* = oesophageal pressure time integral; $\int$Pdi**f* = transdiaphragmatic pressure time integral, * = statistically significantly different from the control condition ($p < 0.01$).

	Rest	NCWR 2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
$\int$Poes**f* (cmH_2O/min)	94 $\pm$ 78	232$\pm$ 44	253$\pm$ 601	268 $\pm$ 48	262 $\pm$ 55	268 $\pm$ 601
$\int$Pdi**f* (cmH_2O/min)	211 $\pm$ 251	223 $\pm$ 83	237 $\pm$ 73	230 $\pm$ 36	265 $\pm$ 62	272 $\pm$ 96
		CWR 2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
$\int$Poes**f* (cmH_2O/min)		213 $\pm$ 105	238 $\pm$ 64	249 $\pm$ 99	233 $\pm$ 84	221 $\pm$ 84
$\int$Pdi**f* (cmH_2O/min)		992 $\pm$ 538	874 $\pm$ 255	959 $\pm$ 391	863 $\pm$ 401*	961 $\pm$ 342*

Work of Breathing

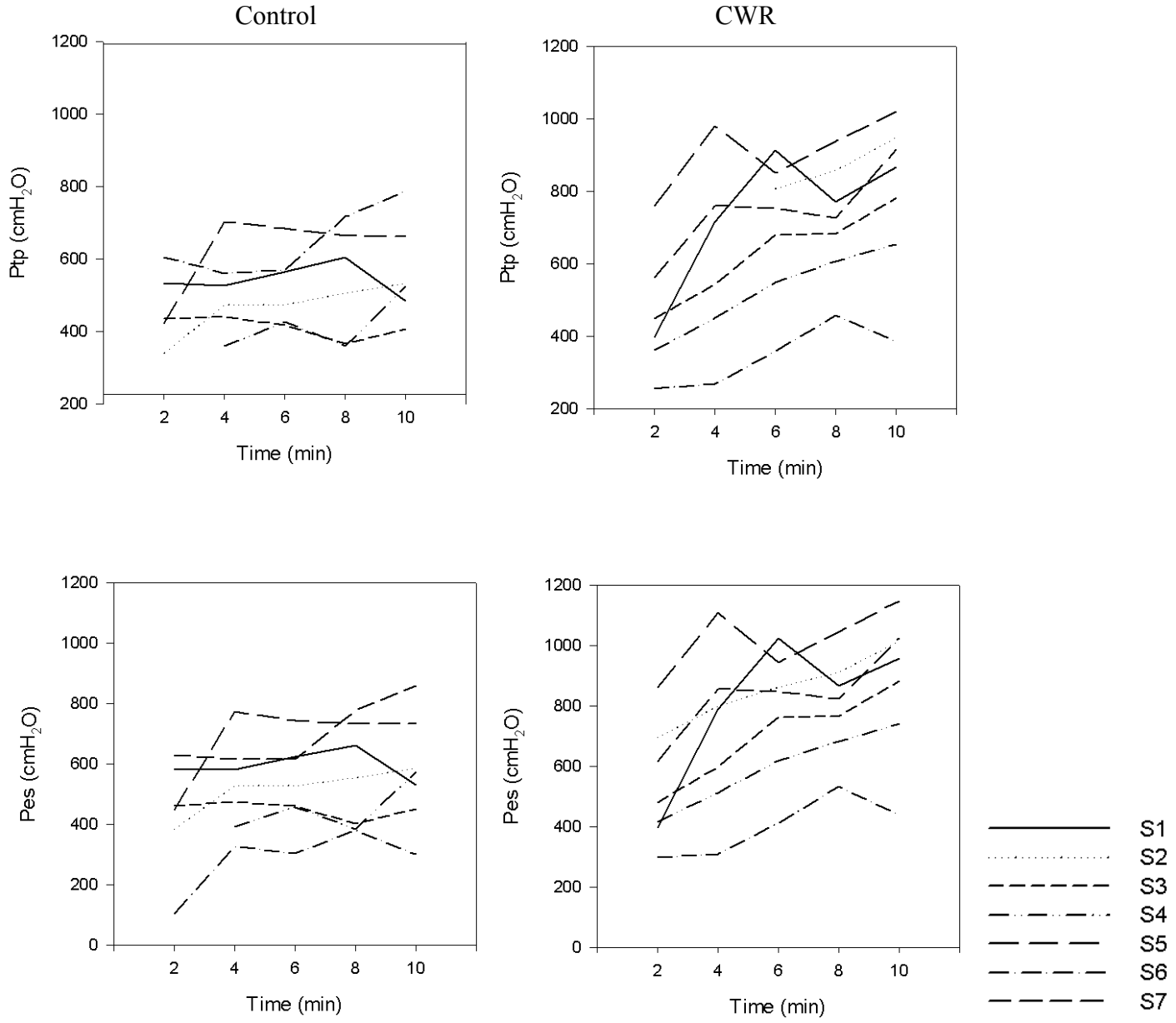
The data for the work of breathing for both the control and the CWR conditions is shown table 8. The work of breathing is partitioned into the work done on inspiration, both flow resistive, and elastic and the resistive work of breathing done on expiration. The total work of breathing reported is the sum of these three components. Flow resistive work on inspiration (268 $\pm$ 83 cmH_2O/min vs. 174 $\pm$ 67 cmH_2O/min and 294 $\pm$ 126 cmH_2O/min vs. 179 $\pm$ 98 cmH_2O/min, $p < 0.05$)

was significantly greater in the CWR condition compared to the control condition in the eighth and tenth minutes. The flow resistive work on expiration and the elastic work on inspiration were not significantly different between the two groups. However, the total work of breathing was significantly greater in the eighth and tenth minute in the CWR condition compared to the control condition (720 ± 159 cmH_2O/min vs. 536 ± 151 cmH_2O/min and 796 ± 216 cmH_2O/min vs. 566 ± 136 cmH_2O/min, $p < 0.05$). Peak inspiratory Poes was significantly lower in the CWR condition compared to the control (-16.3 ± 4.0 cmH_2O/min vs. 21.5 ± 3.4 cmH_2O/min and -16.3 ± 3.0 cmH_2O/min vs. -21.8 ± 3.0 cmH_2O/min, $p < 0.05$) condition at the eighth and tenth minutes. The work of breathing values reported were calculated using Ptp-volume loops however, esophageal pressure-volume loops were also constructed and Figure 8 shows the total work of breathing for individual subjects using both Ptp-volume loops as well as Poes-volume loops.

Table 8. Work of breathing data, partitioned into its components and reported as a total. Reported values are group means and standard deviations. Definition of abbreviations, I (res) = flow resistive work of breathing done on inspiration; E (res) = flow resistive work of breathing done on expiration; I (el) = elastic work of breathing done on expiration; WOBtot = total work of breathing.; Peak Inspiratory Pes = highest recorded oesophageal pressure for that time point during exercise, * = statistically significantly different from the control condition ($p < 0.05$).

	NCWR				
	2 Minutes	4 Minutes	6 Minutes	8 Minutes	10 Minutes
I res (cmH_2O/min)	131 ± 70	114 ± 90	132 ± 62	174 ± 67	179 ± 98
E res (cmH_2O/min)	26 ± 25	68 ± 51	32 ± 20	42 ± 28	46 ± 33
I el (cmH_2O/min)	311 ± 84	337 ± 82	362 ± 61	365 ± 64	343 ± 54
WOBtot (cmH_2O/min)	467 ± 103	510 ± 117	522 ± 102	536 ± 151	566 ± 136
Peak Inspiratory Poes	-21.8 ± 4.4	-22.9 ± 3.8	-22.1 ± 2.5	-21.5 ± 3.4	-21.8 ± 3.0
	CWR				
	2 Minutes	4 Minutes	6 Minutes	8 Minutes	10 Minutes
I res (cmH_2O/min)	150 ± 70	207 ± 90	263 ± 99	268 ± 83*	294 ± 126*
E res (cmH_2O/min)	61 ± 51	124 ± 64	93 ± 72	70 ± 55	131 ± 109
I el (cmH_2O/min)	237 ± 128	310 ± 134	334 ± 109	359 ± 58	371 ± 129
WOBtot (cmH_2O/min)	464 ± 176	620 ± 252	702 ± 192	720 ± 159*	796 ± 216*
Peak Inspiratory Poes	-15.7 ± 4.4	-15.9 ± 3.9	-16.7 ± 4.3	-16.3 ± 4.0*	-16.3 ± 3.0*

Figure 8. Total work of breathing for individual subjects for both the control (left) and chest wall restricted (right) conditions. Top figures are total work of breathing figures for transpulmonary pressure-volume loops while the bottom figures are for oesophageal pressure-volume loops.

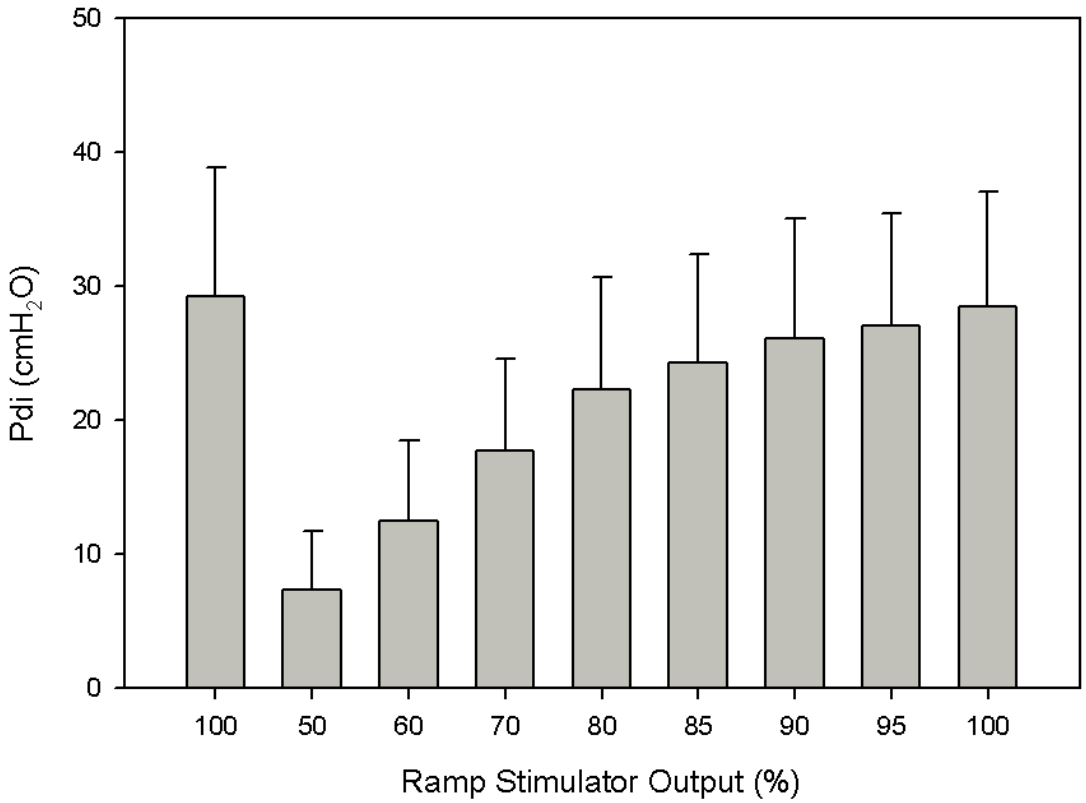


Diaphragm Fatigue

Approximately half of the subjects showed a plateau in their ramp protocol indicating that the cervical magnetic stimulator did not have a sufficient power output to maximally in all instances. A

plateau is indicated by an increase in stimulator output with no further increase in the amplitude of twitch Pdi. Group mean data for the ramp protocol is shown in figure 9. While no plateau is apparent in the group mean data three of the seven subjects did show a plateau (see appendix B, Figure 18 for individual ramp data).

Figure 9. Ramp protocol for all subjects. Bars are group means and error bars are standard deviations.



Individual Data

Individual fatigue data for the potentiated twitches is shown in figure 10 and individual data for non potentiated twitches is shown in figure 11. Ten minutes post control exercise subject 1 showed a 17.9% drop in the twitch Pdi for his potentiated twitches, and a 14.5% drop in his non potentiated twitches. For all other subjects non potentiated twitch Pdi increased from baseline at ten minutes post control exercise. At ten minutes post control exercise no other subjects showed diaphragm fatigue (greater than a 15% drop in twitch Pdi) in their potentiated twitches, however, two subjects showed a drop of about 13% and one subject dropped about 10%. At the 30 minute mark

post control exercise all subjects, except subject 7 (whose potentiated twitches were about 7% below baseline and non potentiated twitches were about 12% below baseline), had returned to baseline or had exceeded baseline. Subject 3 had significantly increased twitch Pdi in both the potentiated and non potentiated twitches at the 10 minute mark post control exercise and so did not undergo the second set of twitches at 30 minutes. Subject 7 on the other hand underwent a third set of post control exercise twitches at 60 minutes to ensure his twitch Pdi had returned to baseline. Subject seven had returned to baseline at the 60 minute mark.

At ten minutes post CWR exercise five of seven subjects showed significant diaphragm fatigue (greater than 15% drop in Pdi post exercise) in both the potentiated and non potentiated twitches for the chest wall restricted condition. All subjects (except subject 7 for non potentiated twitches) had reduced twitch Pdi in both the potentiated and non potentiated twitches. At the 30 minute mark post CWR exercise all subjects twitch Pdi were returning towards baseline. At the 60 minute mark post CWR exercise all subjects except subject 1 had further approached baseline levels for twitch Pdi.

Figure 10. Individual data for the percent change in potentiated twitch Pdi from baseline values. Values are a percent change (increasing or decreasing) starting from the baseline (0). Top figure shows baseline values and 10 and 30 minutes post control exercise. The bottom figure shows baseline values and 10, 30 and 60 minutes post chest wall restricted exercise.

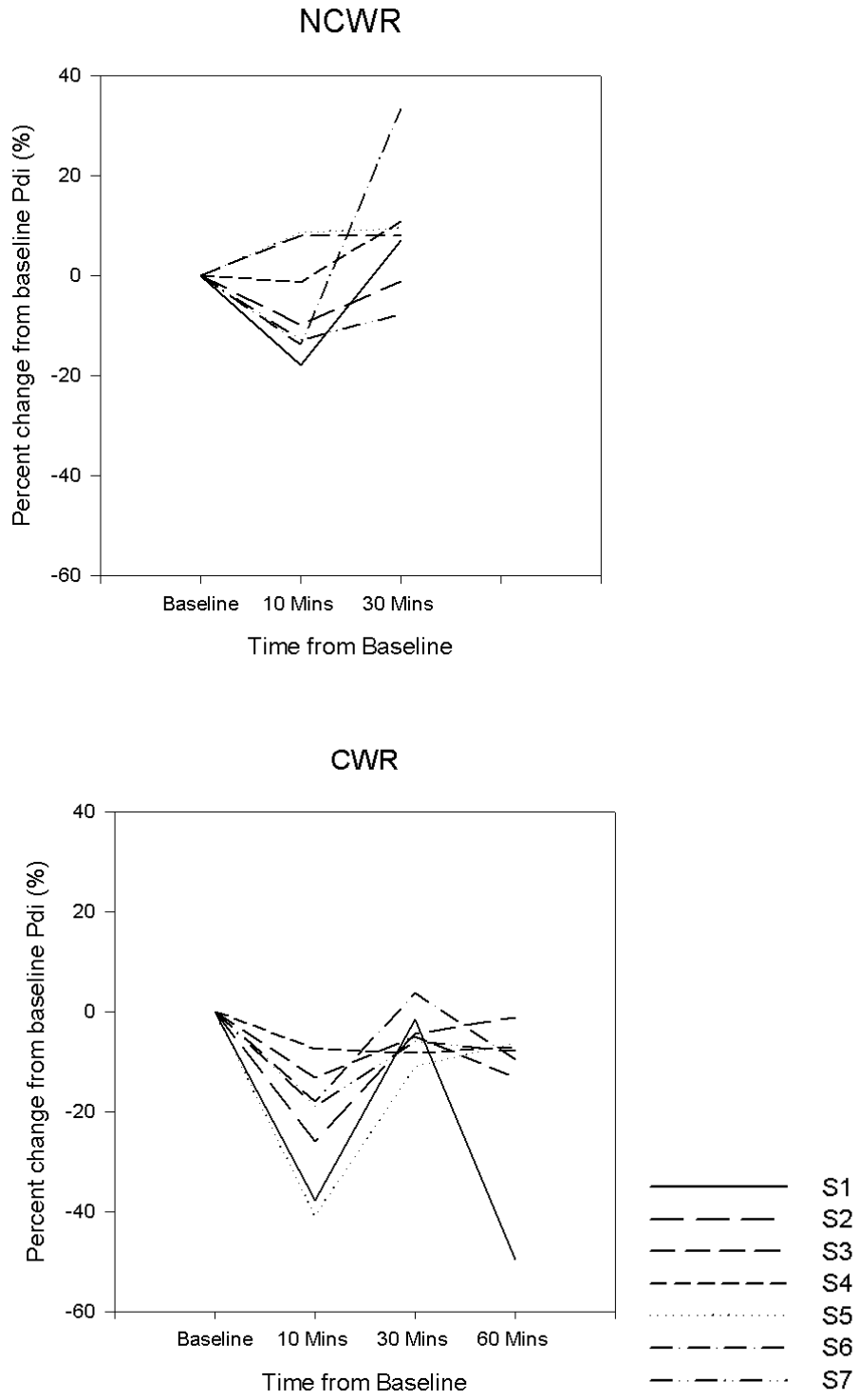
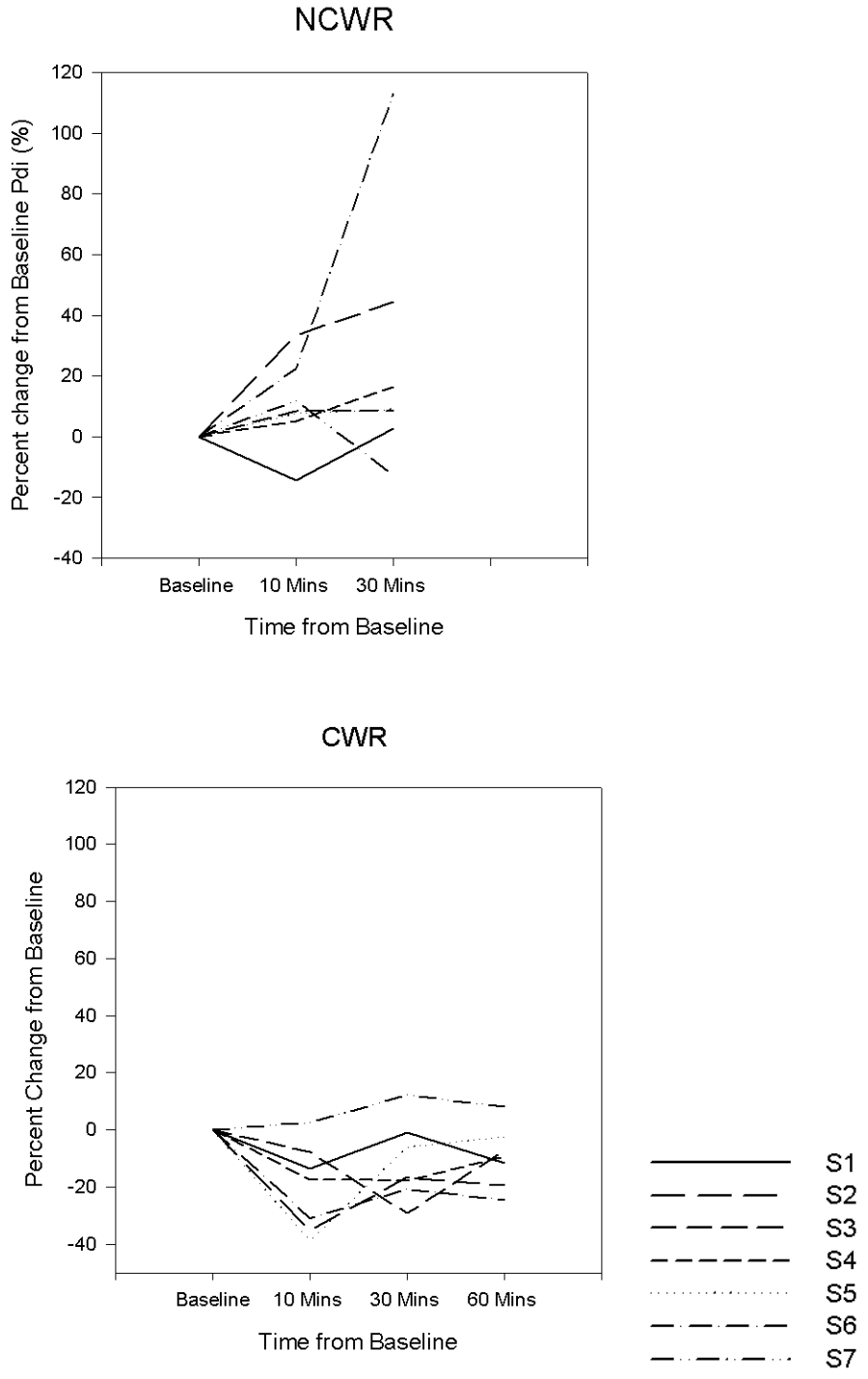


Figure 11. Individual data for the percent change in non potentiated twitch Pdi from baseline. Values are a percent change (increasing or decreasing) starting from the baseline (0). Top figure shows baseline values and 10 and 30 minutes post control exercise. The bottom figure shows base line values and 10, 30 and 60 minutes post chest wall restricted exercise.



Group Mean Data

Potentiated Twitches

Potentiated twitch Pdi group mean data for percent change from baseline is shown in figure 12. Ten minutes post control exercise the mean change in potentiated twitch Pdi was -5.3 $\pm$ 10.8 and at 30 minutes post the mean twitch Pdi had increased by 8.6 $\pm$ 12.8 %. The mean twitch Pdi was not different from baseline at either time point. Ten minutes after CWR exercise the mean drop in potentiated twitch Pdi was -23.3 $\pm$ 12.4% and the mean twitch Pdi was significantly lower than at baseline (36.5 $\pm$ 15.3 cmH_2O vs. 47.4 $\pm$ 16.6 cmH_2O, $p < 0.01$). At 30 minutes post CWR exercise the mean change from baseline was -4.7 $\pm$ 4.7% and was not different from baseline values. At 60 minutes post CWR exercise the mean difference from baseline was -13.6 $\pm$ 16.3% but was not different from baseline.

Potentiated twitches for a representative subject are shown in figure 14. The figure shows three twitches taken before the control exercise (Pre 1, 2 and 3), three twitches taken 10 minutes post control exercise (NCWR 1, 2 and 3) and three twitches taken at 10 minutes post CWR exercise (CWR 1, 2 and 3). The twitches that were used to make this figure are the last three twitches in the group of five that were administered at each time point. It is evident from the figure that there is no difference in twitch amplitude from the pre exercise to 10 minutes post control exercise, but there is a significant different between the baseline Pdi twitch amplitude and the Pdi twitch amplitude taken at 10 minutes post CWR exercise. For this subject there was approximately 40% drop in Pdi twitch amplitude from baseline to 10 minutes post CWR exercise.

Non Potentiated Twitches

The mean non potentiated twitch Pdi ten minute post control exercise increased 10.6 $\pm$ 14.9 % but was not different from baseline. At 30 minutes post control exercise the mean twitch Pdi had increased 25.9 $\pm$ 42.0 % and was different from baseline. For the CWR exercise the mean change from baseline was -20.2 $\pm$ 15.3 % and the group mean was statistically significantly less than baseline (24.6 $\pm$ 8.5 cmH_2O vs. 30.7 $\pm$ 8.6 cmH_2O, $p < 0.05$). At 30 minutes post CWR exercise the mean twitch Pdi was -11.3 $\pm$ 14.0 % but was not significantly different and at 60 minutes post CWR exercise the percent change from baseline was -9.5 $\pm$ 10.7 % and was not significantly different than baseline. The mean data for non potentiated twitch Pdi is shown in figure 13.

Data from an individual subject for single non potentiated twitches is shown in figure 15. The figure shows a single twitch taken before the control exercise (baseline), a single twitch taken 10 minutes post control exercise and a single twitch taken at 10 minutes post CWR exercise. There was no difference in twitch amplitude from the pre exercise to 10 minutes post control exercise, but there is a significant difference between the baseline Pdi twitch amplitude and the Pdi twitch amplitude taken at 10 minutes post CWR exercise. For this subject there was approximately 40% drop in Pdi twitch amplitude from baseline to 10 minutes post CWR exercise.

In this study CMS was used to detect diaphragm fatigue. Unlike electrical stimulation where a muscle can be stimulated at many different stimulation frequencies, CMS only operates at a frequency of one Hz. Based on this stimulation frequency the diaphragm fatigue that was shown in this study was low frequency fatigue.

Figure 12. Group data for the percent change from baseline in potentiated twitch Pdi. Bars represent means and error bars are standard deviations. White bars are post control exercise and grey bars are post chest wall restricted exercise. * = statistically significantly different from baseline ($p < 0.05$).

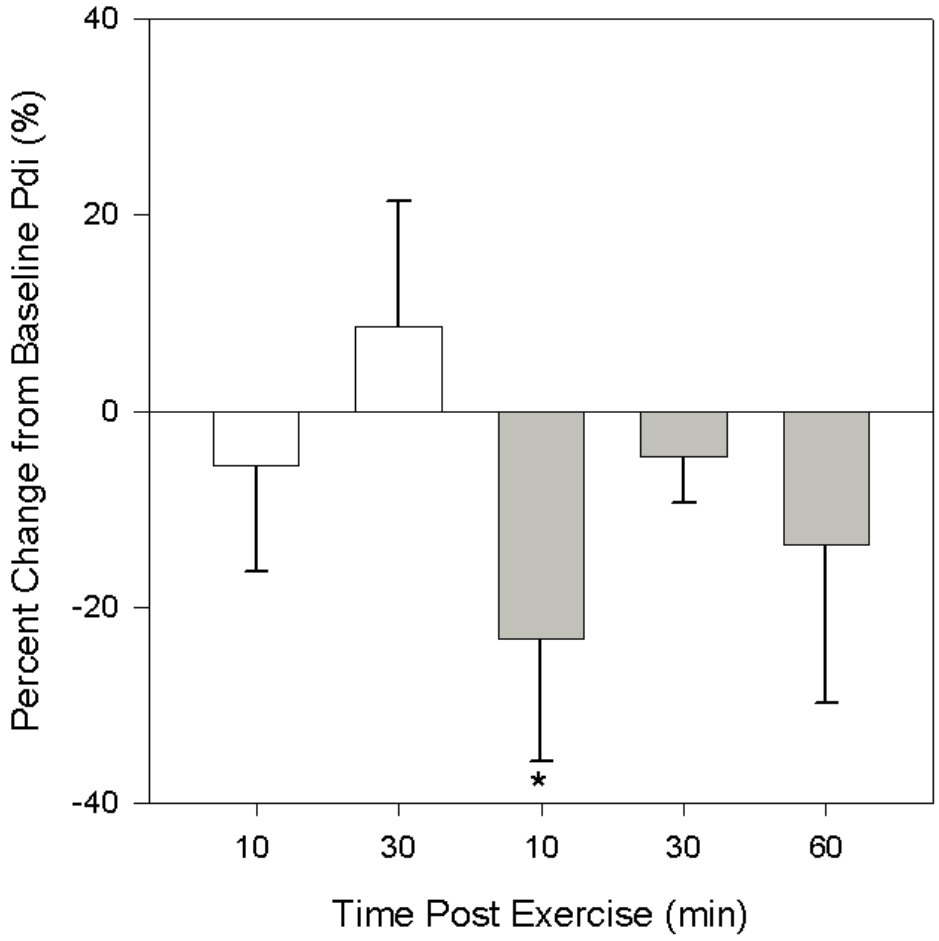


Figure 13. Group data for the percent change from baseline in non potentiated twitch Pdi. Bars represent means and error bars are standard deviations. White bars are post control exercise and grey bars are post chest wall restricted exercise. * = statistically significantly different from baseline ($p < 0.05$).

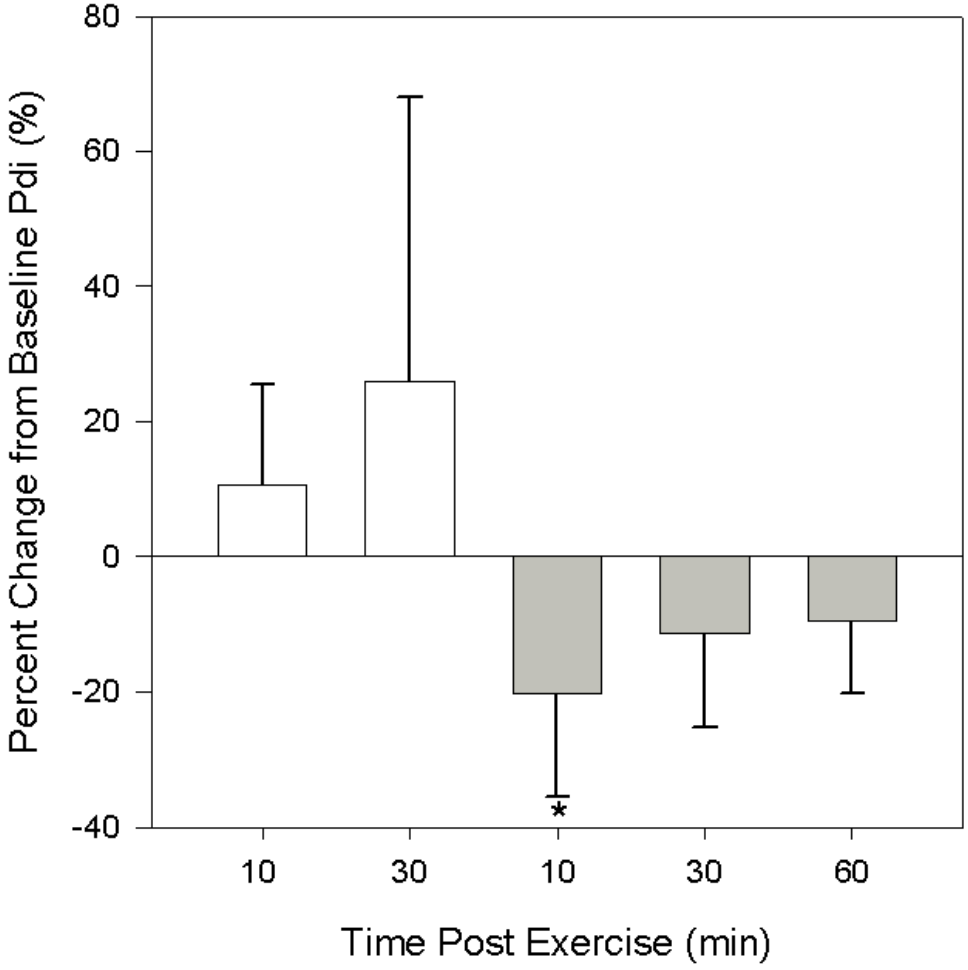


Figure 14. Potentiated twitches from a single subject at baseline, 10 minutes post control exercise and 10 minutes post chest wall restricted exercise. NCWR twitches are at 10 minutes post control exercise and the chest wall restriction twitches are at 10 minutes post chest wall restricted exercise. * = greater than a 25% drop in transdiaphragmatic pressure from baseline twitches, which exceeds the definition of diaphragm fatigue (> 15% decline in Pdi).

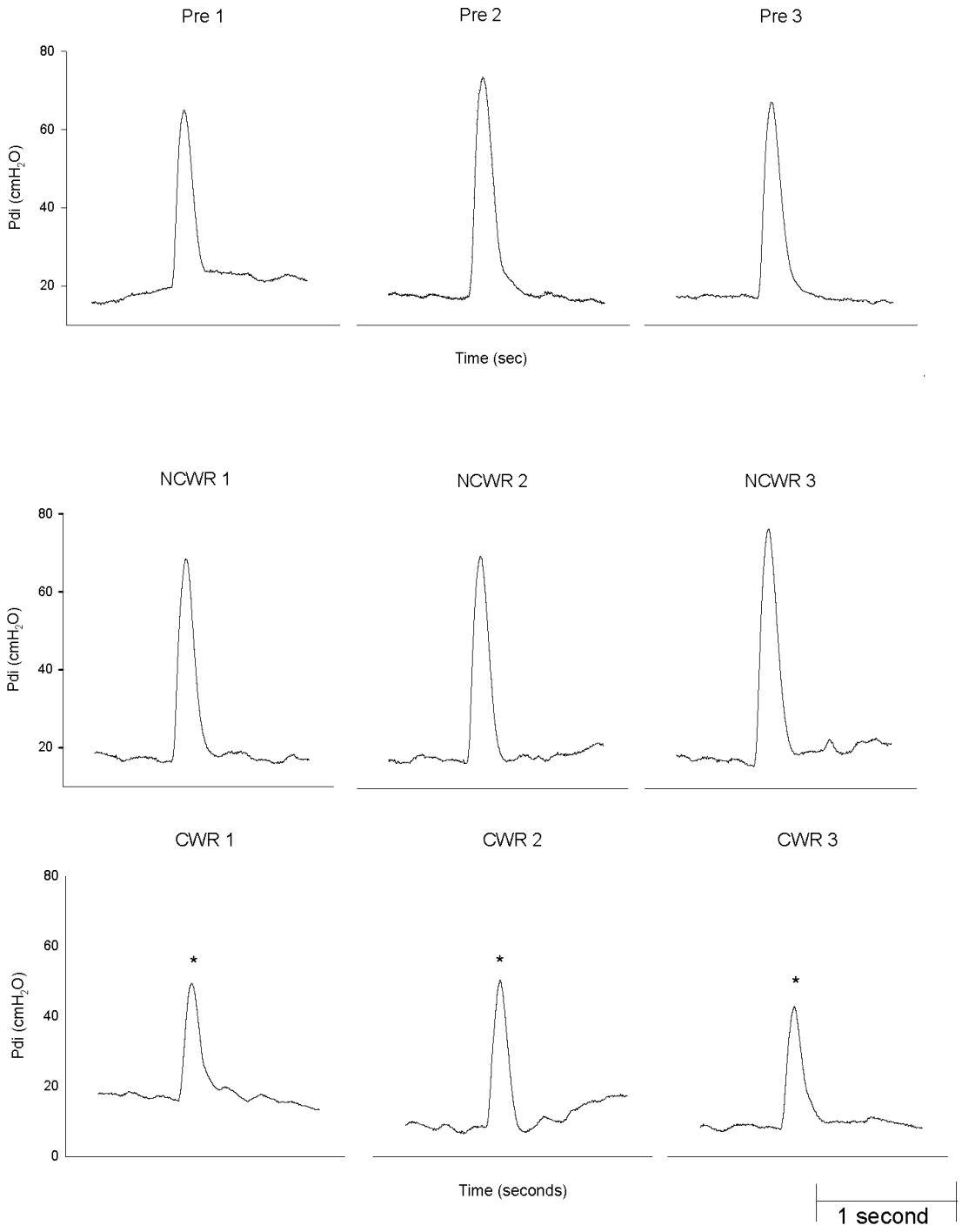
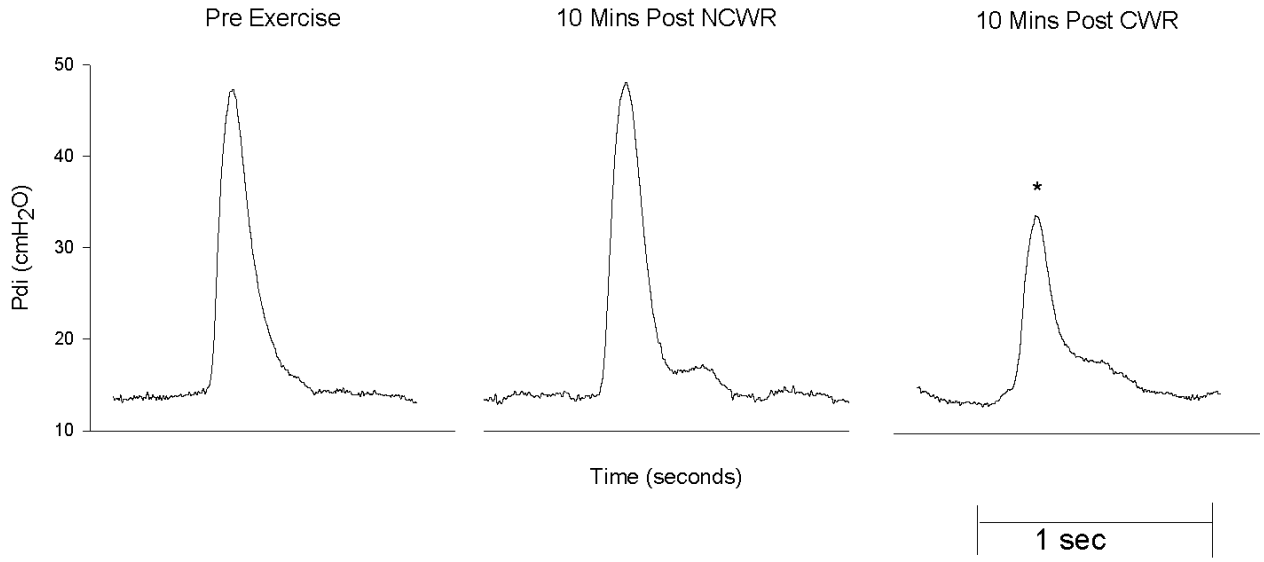


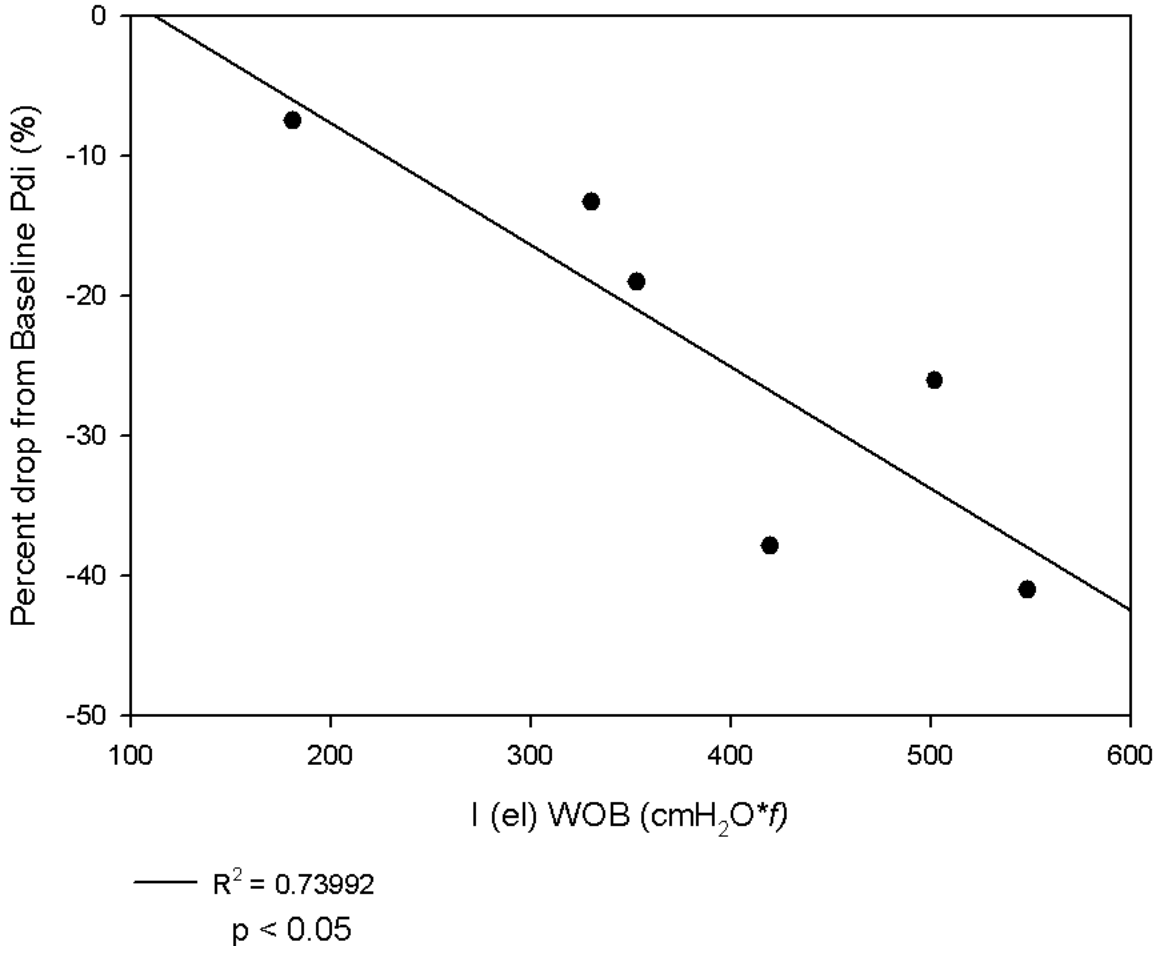
Figure 15. Single non potenitated twitches from an individual subject at baseline, 10 minutes post control exercise and 10 minutes post chest wall restricted exercise. Definition of abbreviation; Pre Exercise = baseline; 10 mins Post NCWR = ten minutes post control exercise, 10 Mins Post CWR = ten minutes post chest wall restricted exercise; Pdi = transdiaphragmatic pressure; * = greater than a 25% drop in transdiaphragmatic twitch amplitude which exceeds the definition of diaphragm fatigue (> 15% drop in Pdi).



Elastic Work of Breathing on Inspiration Vs. Percent Drop in Pdi

Although there was not a significant difference between the elastic work of breathing performed on inspiration (I(el)) between the control exercise and the CWR exercise (see Table 8), the degree of fatigue, or the percent drop in Pdi twitch amplitude from baseline to 10 minutes post CWR exercise was highly negatively correlated to the I(el) ($r = 0.86$). Figure 16 shows the negative linear relationship between the percent drop in Pdi and the I(el), performed on inspiration in the CWR condition. The coefficient of determination (R^2 value of 0.73992 $p < 0.05$) shows that 73% of the variation in the percent drop in Pdi 10 minutes post CWR exercise can be accounted for by the I(el). Furthermore, the two subjects who showed the least amount of fatigue and had the lowest values for I(el) also had the least degree of restriction in their reduction in FVC.

Figure 16. Elastic work of breathing performed on inspiration vs. percent drop in transdiaphragmatic pressure from baseline. Transdiaphragmatic data is taken ten minutes post chest wall restricted exercise and elastic work of breathing on inspiration is taken in the tenth minute of the exercise bout. Definition of abbreviation, I (el) WOB = elastic work of breathing performed on inspiration, R^2 = 0.73992



DISCUSSION

The purpose of this study was to determine if CWR during low intensity exercise would result in diaphragm fatigue. To perform this investigation healthy subjects underwent two exercise bouts at 45% of their peak power output, one with no restriction of the chest wall and one with restriction straps applied around the chest wall and abdomen. The restriction in this study replicated the lung volumes and breathing mechanics of restrictive disorders. The main findings of this investigation are three fold. First, cycle exercise with CWR caused significant diaphragm fatigue. Second, there were significant changes in the breathing patterns and operational lung volumes during CWR exercise compared to control exercise. Third, the work of breathing was significantly greater in CWR exercise compared to control exercise and that the degree of diaphragm fatigue was associated with increased inspiratory elastic work of breathing.

Chest Wall Restriction as a Model

Chest wall restriction has been used in healthy people to mimic restrictive disorders of the chest wall, such as, kyphoscholiosis, pectus excavatum, ankylosing spondylitis, which involve deformities of the chest wall, as well as, chronic heart failure (Coast and Cline 2004, Harty et al., 1999; Hussain et al., 1985; Miller et al., 2002, O'Donnell et al., 2000), and infiltrative parenchymal diseases (interstitial lung disease), where there is an accumulation of fluid in the lungs, or fibrosis of lung tissue (O'Donnell et al., 2000). Chest wall restriction was used in this study to effectively replicate these restrictive conditions; this is evident from, the reductions in resting and operational lung volumes, the tachypneic breathing patterns and the high work of breathing elicited in CWR exercise. Resting and operational lung volumes are reduced in these patient groups, as well; high V_T/IC ratios and tachypnea at relatively low exercise intensities are characteristic of these disorders (Hsia 1999; O'Donnell et al., 1998 and 2000). Chest wall restriction in healthy people has been shown to accurately replicate the reduction in resting and operational lung volumes (FVC, IC, IRV, EELV, and EILV) as well as the breathing patterns seen in patients with restrictive disorders (Cline and Coast 2004, Miller et al., 2002 and O'Donnell et al., 2000). In the present study, CWR was accomplished with the use of inelastic straps that were tightened as the subjects exhaled to RV. The degree of restriction used, approximated the lung volumes and breathing mechanics that characterize restrictive conditions (Johnson et al., 2000; Kufel et al., 2002; Mancini 1995; O'Donnell et al., 1998;

Olson et al., 2006b) See appendix B, Table 28 for a comparison of this study with other CWR studies and studies involving restrictive disorders.

In the present study subjects experienced, on average a 40% reduction in FVC, this is a similar degree of restriction reported in restrictive syndromes (Johnson et al., 2000; Kufel et al., 2002; Mancini 1995; O'Donnell et al., 1998; Olson et al., 2006b). In this study, the size of the MFVL of all subjects in the CWR condition, were significantly reduced compared to the control condition, resulting in a decline in the peak expiratory flow rates. Furthermore, the shape and size of the MFVL of the CWR subjects, in this study, were comparable to those found in individuals with chronic heart failure (Johnson et al, 2000). Resting lung volumes (IC, IRV and V_T) were reduced in the CWR condition of this study. This resulted in an inability to increase V_T during exercise as the V_T/IC ratio was increased and the IRV available to increase the size of V_T was insufficient. Furthermore, the magnitude of the reductions in this examination were similar to those reported in individuals with restrictive disorders (Johnson et al., 2000; Kufel et al., 2002; Mancini 1995; O'Donnell et al., 1998; Olson et al., 2006b).

Operational lung volumes (EELV and EILV) during the CWR exercise in this study were also decreased, and these reductions were similar in magnitude to individuals with restrictive disorders, who breathe at reduced FRC (Johnson et al., 2000; Kufel et al., 2002; Mancini 1995; O'Donnell et al., 1998; Olson et al., 2006b), and to chronic heart failure patients who breathe close to RV at rest. Additionally, individuals with chronic heart failure do not tend to increase their EELV during exercise and therefore, they experience severe EFL as exercise progresses (Johnson et al., 2000; Olson et al., 2006b). In this study subjects had reduced EELV throughout the CWR exercise condition and all subjects showed some degree of EFL. However, in some subjects EELV increased near the end of exercise resulting in dynamic hyperinflation (see appendix B, Figure 17). These reductions in resting and operational lung volumes lead to a rapid and swallow breathing pattern in the CWR condition of this study, and a reduced V_T and increased breathing frequency were present throughout the CWR exercise condition. This tachypneic breathing pattern is characteristic of individuals with restrictive conditions and may contribute to an increased work of breathing (Johnson et al., 2000, Kufel et al., 2002; Mancini 1995; O'Donnell et al., 1998; Olson et al., 2006b).

Reductions in the operational lung volumes as seen in, individuals with restricted disorders, results in an increase in the total work of breathing and alters how it is distributed with respect to the elastic and flow resistive work. Breathing at reduced FRC results in a reduction of the elastic work of

breathing, however, the flow resistive work of breathing is consequently increased (Hlastala and Berger 1996; Olson et al., 2006b). Nonetheless, the total work of breathing is increased when the diaphragm is not at its optimal length (FRC) for force production (NHLBI Workshop Summary 1990). This same pattern in the division of the work of breathing was shown to occur in the CWR subjects of this investigation (see results, Table 8).

Physical restriction of the chest wall is often accompanied by an increase in the respiratory drive due to the ventilatory stimulation effects of having a high physiological dead space (O'Donnell et al., 2000). The combination of restriction and increased respiratory drive during exercise can augment ventilatory limitations and accelerate the arrival of intolerable dyspnea and consequently exercise intolerance (O'Donnell et al., 2000). O'Donnell et al. (2000) stated "Thoracic restriction [in healthy people] gave rise to discrete qualitative sensations of inspiratory difficulty, unsatisfied respiration, and shallow breathing, which have been shown previously to characterize restrictive disorders." O'Donnell et al., goes further to make the conclusion that the "unpleasant respiratory sensations" may have their physiological basis in a reduced capacity to increase lung volume and move the chest cavity appropriately when ventilatory drive is enhanced. The high degree of exertional dyspnea in individuals with restrictive disorders may lead to exercise intolerance.

In a study examining the exercise tolerance of individuals with ankylosing spondylitis, Elliot et al., (1985) found that subjects with the condition who consequently suffered from CWR showed a reduced VO_{2MAX} when compared to healthy age matched controls. However, they concluded that the reduction in VO_{2MAX} was most likely due to deconditioning or due to cardiovascular limitations rather than ventilatory impairments. Inducing CWR in healthy people might not necessarily mimic the cardiovascular limitations that occur in individuals with restrictive disorders such as ankylosing spondylitis. However, if the cardiovascular restrictions are related to reductions in intrathoracic space and the resulting reductions in cardiac output, than CWR might approximate these impairments, (Miller et al., 2002, Olson et al., 2006a). In 2002, Miller et al. showed that cardiac output was significantly reduced when subjects exercised with CWR compared to unrestricted control exercise.

Chronic heart failure has been shown to display some characteristics of restrictive lung disease, such as, reduced lung volumes and altered breathing patterns at rest and during exercise (Johnson et al., 2000; Mancini 1995; Olson et al., 2006b). It has been shown that patients with chronic heart failure have significantly larger hearts, approximately double the size of healthy-age matched controls. These significantly larger hearts consume a much greater portion of the thoracic

container proportionally, and may present problems to the patient in the form of reduced lung volumes and tachypneic breathing patterns (Olson et al., 2006a). Furthermore, a clear relationship has been established between increases in cardiac volume and reductions in lung volumes (Olson et al., 2006a). Chest wall restriction in healthy people has been shown to mimic these characteristics of chronic heart failure (Miller et al., 2002; O'Donnell et al., 2000).

There are other aspects of restrictive lung disease that CWR in healthy people cannot replicate, such as, the loss of function of alveolar-capillary units, secondary hemodynamic and cardiac dysfunction and a reduced lung diffusion capacity (Hsia 1999). Therefore, it is important to remember the limitation of studies involving CWR in healthy people when generalizing the results.

Conversely, CWR may also result in physiological changes that are not necessarily present in restrictive lung diseases, such as, exaggerated bronchoconstriction (Torchio et al., 2006). When methacholine was given to subjects who were CWR, airway responsiveness to the methacholine challenge was increased. Torchio et al., (2006) speculated that when breathing at low lung volumes induced by CWR, the narrowing of the airways was enhanced due to the adaptation of airway smooth muscle to a length at which the contractile proteins are able to generate a force greater than normal.

Diaphragm Fatigue

This is the first study to investigate the relationship between diaphragm fatigue and CWR in subjects exercising at a low intensity. A significant drop in Pdi twitch amplitude, (> 15% reduction) indicating that the diaphragm fatigued, occurred 10 minutes post CWR exercise, in this study. The degree of fatigue found in this study was similar in magnitude to other diaphragm fatigue studies in which subjects exercised at intensities greater than 80 - 85% of their peak power output until exhaustion (Babcock et al., 1995, 1996, 1998 and 2002; Johnson et al., 1993; Mador et al., 1993). In this study subjects exercised at 45% of their peak power output for ten minutes, an intensity of about half of that reported in the above mentioned diaphragm fatigue studies. In this study however, the FVC of subjects were restricted by about 40% using inelastic straps, this resulted in a significantly increased work of breathing, which was associated with the development of diaphragm fatigue. This association between the work of breathing and diaphragm fatigue was strengthened by the high correlation between I(el) and the percent drop in twitch Pdi (10 minutes post CWR exercise). Furthermore, in this study the $\int Pdi * f$ that was shown to occur in CWR exercise was approximately double of that previously reported in other fatigue studies in which subjects exercised at

approximately double the intensity (Babcock et al., 1995 and 1996). This suggests that the force production of the diaphragm was very high, which allowed fatigue to occur despite the fact that the cardiac output may have been reduced.

Diaphragm fatigue has also been shown to occur in subjects performing resistive breathing till task failure. Roussos and Macklem (1977), had subjects breathe against a resistance at a predetermined percentage of their maximum Pdi until they could no longer maintain that Pdi for five breathes. It was shown that subjects could maintain breathing at a Pdi below 40% of their maximum Pdi indefinitely, if EELV remained at FRC. However, if Pdi was greater than 40% of the subjects maximum, fatigue would eventually ensue (Roussos and Macklem 1977). When subjects were asked to mimic the breathing patterns (breathing frequency, V_T and $\int Pdi*f$) and timing seen during exercise, however, diaphragm fatigue did not occur (Babcock et al., 1995). In fact, when mimicking breathing patterns at rest the $\int Pdi*f$ required to cause fatigue was 80% greater than that during exercise. Therefore, the pressure production of the diaphragm during whole body endurance exercise did not result in fatigue at rest. When replicating the exercise breathing patterns at rest the diaphragm receives a significant portion of the cardiac output making fatigue less likely. When performing hyperventilatory tasks at rest the respiratory muscles have been estimated to receive about 30% of the total cardiac output, however, during high intensity exercise this is reduced to 10-12% (Aaron et al., 1992).

In this study, it is possible that the diaphragm was receiving less total blood due to the physical restriction of the chest wall, which may result in reductions to cardiac output (Miller et al., 2002). In 2002, Miller et al. showed significant reductions, (about 2-3L/min) in cardiac output during CWR exercise at 45% of VO_{2MAX} compared to the control condition. This suggests that blood flow to the diaphragm is significantly reduced. Furthermore, they showed that the left ventricular filling and emptying rates were significantly reduced at a given heart rate in the CWR condition compared to the control condition. Stroke volume was significantly reduced and heart rate was significantly increased in the CWR condition compared to the control. In our study we did not measure stroke volume and therefore have no measure of cardiac output, however, based on the similarity of the results between this study and the Miller et al. study and given that the same testing procedures were used in the two studies, the assumption that the subjects in this study would show a similar pattern as those in the Miller et al. study can be made. Nevertheless, unlike in the Miller et al., (2002) study there was no difference in heart rate between the control condition and the CWR condition in this study.

Despite the changes in cardiac output in the Miller et al., (2002) study, there was evidence to suggest that insufficient blood flow did not play a role in the observed diaphragm fatigue in this study. $PaCO_2$ levels are closely related to blood flow, if $PaCO_2$ increases then blood flow increases, and if $PaCO_2$ decreases, blood flow decreases. In this study there was no difference in $PetCO_2$ between the control and CWR conditions suggesting that the fatigue did not occur do to a lack of blood flow and that the fatigue most likely occurred due to the very high work of the diaphragm present in the CWR exercise condition. Furthermore, a high correlation between I(el) and the percent drop in twitch Pdi 10 minutes post CWR exercise was found in this study providing greater evidence that reductions in cardiac output, or a lack of sufficient blood flow were not mechanisms for fatigue. Despite the fact that there was no difference between the control and CWR conditions for I(el), the correlation between I(el) and percent drop in Pdi was very high. This association strengthens the argument that reducing the compliance of the chest wall forces subjects to exert a significantly greater Pdi in order to produce the same change in volume. This is indicated by the significantly higher $\int Pdi*f$ in the CWR compared to the control condition. In this study, despite all subjects being close to 40% restricted the degree of I(el) varied tremendously. However, the two subjects with the lowest I(el) were also the least restricted. Moreover, the breathing pattern between subjects was not identical and the two subjects who had the highest I(el) also displayed two of the highest breathing frequencies and largest V_E throughout the CWR exercise.

Exertional Dyspnea

The dyspnea ratings in this study were significantly higher in the CWR condition than in the control condition despite there being no difference in the ratings of leg discomfort between the two conditions. Additionally, the RPE values for dyspnea in the CWR submaximal exercise were approaching the RPE values for dyspnea recorded at the end of the maximal aerobic test (see results, Figure 4). Furthermore, the levels of dyspnea that were found in the CWR condition of this study were the same as those that have been reported in individuals with interstitial lung disease, during symptom limited incremental cycle exercise (O'Donnell et al., 1998). This is interesting given that in individuals with interstitial lung disease, adaptation to the restrictive abnormalities present with the disease, may have been occurring for years.

Dyspnea can also be influenced by an increase in the force production of the respiratory muscles, as well as, alterations in the patterns of force production; through, changes in velocity,

breathing frequency, and duty cycle (Romer and Polkey 2008). In this study the force production of the diaphragm in the CWR condition was significantly increased compared to the control condition, as evidenced by the significantly higher ∫Pdi*f. There was also an increase in the velocity of shortening of the diaphragmatic muscle fibers and an increased breathing frequency. Additionally when breathing at significantly reduced lung volumes (as seen in the 40% reduction in FVC in this study) the muscle fibers of the diaphragm are put at a significantly shorter operating length; this results in a considerable disadvantage for force production and can play a large role in the development and the degree of dyspnea. Individuals with restrictive disorders often report sensations of exertional dyspnea. In 1998, O'Donnell et al. stated that in individuals with interstitial lung disease the intensity of dyspnea was more closely related to the mechanical constraints on volume expansion than to inspiratory effort.

It has also been suggested that the force production of the diaphragm, indicated by the time integral of Pdi, increases at the beginning of exercise. This is followed by a stabilization or decrease as exercise progresses despite increases in V_E and ∫Poes*f (Babcock et al., 1998). These changes in the time integrals of Pdi and Poes, and the V_E, may indicated that the relative contribution from the diaphragm to total inspiratory effort declines as high intensity exercise is maintained (Babcock et al., 1998). In this study despite the exercise intensity being very low it was found that the highest levels of ∫Pdi*f occurred in the first two minutes, followed by a decline. The time integral of Pdi rose again in the tenth minute, however, it did not increase to the level recorded in the second minute. Furthermore, in some subjects there was a reduction in ∫Pdi*f during the final stages of the CWR exercise bout (see appendix B Table 22). This may indicate that in this study, the relative contribution of the diaphragm to overall inspiration decreased as exercise was prolonged. A reduction in the relative contribution of the diaphragm to inspiration over time resulting from diaphragm fatigue has been well documented (Romer and Polkey 2008). Due to the reduction of diaphragmatic force output, accessory muscles of inspiration are recruited in order to facilitate the progressive hyperventilatory response required to maintain or increase the ventilatory demand during exercise (Babcock et al., 1995 and 1996; Johnson et al., 1993). This reliance on accessory muscles as exercise continues may result in further distortion of the chest wall (Goldman et al., 1976; Grimby et al., 1976) reductions in mechanical efficiency of breathing and ultimately result in increases in metabolic and blood flow demands of these muscles (Romer and Polkey 2008). Furthermore, the recruitment of accessory muscles of inspiration results in increased sensory input being sent to the central nervous

system. This ultimately could result in an enhancement of the sensations of dyspnea (Supinski et al., 1987; Suzuki et al., 1992; Ward et al., 1988).

Causes and Types of Fatigue

Failure of the excitation-contraction coupling mechanism has been recognized as one of many potential causes of fatigue in skeletal muscles; however, there are many components of the excitation-contraction coupling mechanism where this may occur. Propagation along the surface membrane and/or the t-tubule of the action potential (Edwards et al., 1977), failure of the coupling mechanism between the action potential and calcium release, or a collapse of the regulation of calcium at the level of the contractile proteins are components of the excitation-contraction coupling mechanism where failure could occur (Westerblad et al., 1990).

Fatigue can also be classified based on whether it is central or peripheral. Central fatigue results when the force of a contraction decreases due to a fall in motoneuronal output from the central nervous system. Peripheral fatigue occurs when there is failure at the neuromuscular junction and can be assessed as a reduction in the motor force output or velocity in response to electrical or magnetic stimulation. (American Thoracic Society/European Respiratory Society, 2002). There are two types of peripheral fatigue, one in which there is a loss of force at high frequencies of stimulation (50-100Hz), and one in which there is a loss of force at low frequencies of stimulation (<20Hz), called high and low frequency fatigue respectively (Jones 1996).

Low frequency fatigue has been demonstrated in humans exercising at high intensities till exhaustion (Babcock et al., 1995; Johnson et al., 1993; Levine and Henson 1988) and high frequency fatigue has been reported to occur in humans performing resistive breathing till task failure (Aubier et al., 1981; Yan et al., 1993), as well as, after high intensity exercise (Babcock et al., 1998). In this study, however, since CMS was used to assess diaphragmatic force production assessment could only occur at 1Hz. Therefore, as a method for detecting diaphragm fatigue, CMS is unable to test for the presence of high frequency fatigue. Furthermore, since post exercise tests were performed ten minutes after the completion of exercise the likelihood of detecting high frequency fatigue is low, as muscles tend to recover quickly from it. Therefore, the diaphragm fatigue present in this study was low frequency fatigue.

The recovery from low frequency fatigue is slow and may take minutes to hours (Mancini 1995) or in severe cases days (Jones 1996). In this study recovery occurred in about 30 minutes, in

most subjects. In 1998, Babcock et al., showed recovery from low frequency fatigue 60 minutes after the completion of a high intensity exercise bout till exhaustion, while Laghi et al., (1995) showed the presence of low frequency diaphragm fatigue up to 24 hours after subjects performed inspiratory resistive loading, till task failure.

Low frequency fatigue may be the consequence of structural damage to the muscle fibers and/or damage to the excitation-contraction coupling mechanism. The slow recovery from low frequency fatigue may be due to the necessity to repair the muscle, which is reliant on protein turnover (Jones1996). It is also possible that the loss of force at low frequencies may be explained by a reduction in calcium released from the sarcoplasmic reticulum (Westerblad 1990; Jones 1996) or by reductions in the calcium sensitivity of troponin (Jones 1996). Westerblad et al., (1993) showed that there was a reduced intracellular calcium concentration for a given stimulation frequency in fatigued muscle fibers while there was no evidence of altered intracellular buffering of calcium and the relationship between tension and intracellular calcium had not changed. Therefore, the cause of low frequency fatigue in these preparations was most likely the results of a reduced release of calcium from the sarcoplasmic reticulum rather than a decreased binding of calcium to troponin. In this study, although measures of the intracellular calcium concentrations were not made, the low frequency fatigue was most likely due to a loss in the release of calcium from the sarcoplasmic reticulum. This is supported by the Pdi twitch values returning to baseline, 30 minutes after the completion of CWR exercise (Babcock et al., 1998). When recovery from fatigue is very slow, like in the Laghi et al., (1995) study it is more likely that the mechanism of fatigue is related to damaged muscle fibers (Babcock et al., 1998). Whereas, low frequency fatigue that recovers relatively quickly is most likely due to decreases in the release or concentrations of intracellular calcium (Babcock et al., 1998).

The Work of Breathing

In this study the total work of breathing was significantly greater in the CWR exercise condition compared to the control condition, in both the eighth, and tenth minute, and it was comparable to values reported in other CWR studies (Miller et al., 2002). Partitioning the work of breathing into three components, I(res), E(res) and I(el) showed where the differences in the work of breathing, between the two conditions, occurred. The CWR exercise condition was significantly higher in I(res) but not in E(res) or I(el). This finding is in accordance with what has previously been shown to occur in other CWR studies (Miller et al., 2002). Furthermore, like individuals with

restrictive lung disease the subjects in this study were breathing at reduced FRC. Individuals with restrictive lung disease have an increased elastic work of breathing with no changes in flow resistive work of breathing, however, they breath at lower FRC to reduced the elastic work of breathing. The consequence of breathing at a lower FRC, however, is an increase in the flow resistive work of breathing (Hlastala and Berger 1996; Olson et al., 1996b).

Despite no difference in the I(el) between the two conditions there was a significant linear correlation between the I(el) in the CWR condition and the degree of fatigue ten minutes post CWR exercise. This association suggests that a high elastic work of breathing on inspiration is an important contribution to diaphragm fatigue in CWR subjects exercising at low intensities. However, caution must be emphasized, as the presence of a correlation does not indicate causation.

The Pdi time integrals were also significantly greater in the CWR exercise condition compared to the control condition despite the exercise intensity being the same. This indicates that the diaphragm produced significantly greater force in the CWR exercise condition compared to the control condition to produce the same levels of ventilation. Furthermore, the time integrals of Pdi found in this study were approximately double of that reported in other diaphragm fatigue studies in which unrestricted subjects exercise at very high intensities (80-85% ofVO_{2MAX}). Therefore, in the CWR condition of this study, despite exercising at intensities of about half of that in other diaphragm fatigue studies, the diaphragm worked twice as hard. The $\int Pdi*f$ can also be used as an indication of the degree to which the diaphragm is contributing to inspiration (Babcock et al., 1998). At the beginning of high intensity exercise the $\int Pdi*f$ increases and therefore the contribution the diaphragm is making to inspiration increases. However, as high intensity exercise progresses the $\int Pdi*f$, has been shown to decrease, despite the $\int Poes*f$ and V_E increasing. This indicates that the relative contribution of the diaphragm to inspiration decreases and that accessory muscles of inspiration must be recruited to maintain and increase V_E levels (Babcock et al., 1998). It has been suggested that this leveling off of diaphragmatic force output may be due to the presence of high frequency fatigue in the diaphragm (Babcock et al., 1998). In 4 of the 7 subjects in this study the $\int Pdi*f$ decreased at the end of exercise (see appendix B, Table 22).

Operational Lung Volumes and Breathing Patterns

In this study, the FVC was successfully reduced by 40% with CWR. This level of restriction is similar to the level of restriction described in other CWR studies (Miller et al., 2002, O'Donnell et

al., 2000). Furthermore the absolute FVC of the subjects in this study were similar to those reported for individuals with restrictive disorders (O'Donnell et al., 1998 and 2000). We also saw a 30% reduction in IC, which was similar to what has been reported in the literature (O'Donnell et al., 2000). During the CWR condition subjects had significantly reduced EELV and EILV compared to the control condition. These reductions in lung volumes may have contributed to the increased work of breathing seen in the CWR condition. The work of breathing increases when the diaphragm is not at its optimal length for force production, as occurs when breathing at volumes below FRC. Therefore, the muscle fibers need to produce greater force in order to overcome the disadvantaged fiber length and produce a contraction.

The size of the MFVL in the CWR condition was significantly reduced for all subjects, and all subjects had a reduced FVC and peak expiratory flow rates (see results, Figure 7 and appendix B, Figure 17). During CWR exercise, tidal breaths consumed a much larger portion of the MFVL compared to the control condition and EFL was present to some degree in all subjects. Furthermore, some subjects demonstrated an increase in EELV, which represents dynamic hyperinflation, allowing them to access higher flow rates. Miller et al., (2002) showed dynamic hyperinflation in subjects who were CWR and exercising at 45% of VO_{2MAX}, they did not, however, show any EFL. Miller et al., makes the assumption that the dynamic hyperinflation was the result of EFL.

In this study, CWR subjects had significantly reduced IRV due to the reduction in FVC, and during exercise had significantly increased V_T/IC ratios, indicating that the subjects could not significantly increase the size of their tidal breaths. Furthermore, the V_T in the CWR exercise was significantly reduced compared to the V_T during the control exercise, and the breathing frequencies were significantly increased. Chest wall restricted subjects therefore, displayed the tachypneic breathing pattern previously described in CWR subjects and which is characteristic of restrictive disorders (Miller et al., 2002, O'Donnell et al., 2000).

Limitations and Technical Considerations

Lack of Twitch Pdi Plateau in Ramp Protocol

A plateau in twitch Pdi during the ramp protocol was shown in three of seven subjects (see appendix B, Figure 18). In the subjects that did not show a plateau it is probable that the diaphragm was not being supramaximally stimulated. Supramaximal stimulation is important because it indicates that any further increase in the intensity of the stimulus will not result in an increase in the

force production of the diaphragm. Therefore, the tension that is generated is in a constant relationship with maximal tetanic tension and any reduction in force production after exercise reflects a real decrease in the amplitude of a single twitch (Man et al., 2004). In the absence of supramaximal stimulation it is possible that other factors could have lead to the reductions in the amplitude of twitch Pdi post CWR exercise. However, all the subjects in this study were stimulated at 100% of stimulator output for the entire duration of their test. Furthermore, other studies have failed to show a plateau in twitch Pdi when using CMS to stimulate the diaphragm (Mador et al., 1996). In 1996, Mador et al. failed to show a plateau in twitch Pdi or M-waves when using CMS to stimulate the diaphragm. They note that there was a 10% increase in the twitch Pdi when the CMS was increased from 90% to 100%. However, they also note that maximal stimulation only occurs at the highest power outputs (>90%) and therefore, it is difficult to demonstrate a plateau. It is also noted that the M-wave amplitude at maximal CMS stimulation was similar to those achieved when using transcutaneous stimulation. In another study done by Mador et al., (2002) it was noted that when using CMS a plateau in twitch Pdi was not apparent until approximately 95% of stimulator power output.

Excessive Electrocardiographic Artifact in the Oesophageal Pressure Trace

In many of the subjects in this study a significant ECG artifact obscured the Poes trace. This interference in the Poes signal made it difficult to determine if the twitches were delivered at FRC. To overcome this problem and determine if twitches had in fact been delivered at FRC, and should therefore be included in analysis, several steps were taken. The Poes signal was examined to determine if the twitch occurred at the end of the convex portion of the breath (the end of the breath out). The mean of the oscillating deviations in the Poes signal was taken immediately prior to the twitch. The average Poes signal for the second before the twitch was delivered was also determined. The amplitude of the twitch Pdi was recorded and twitches were excluded based on the following criteria. 1) The Pdi twitch amplitude was not within $\pm$ 10% of the other twitches in the group. 2) The twitch was not delivered at the end of the convex portion of the Poes curve and 3) the one second average of Poes before the twitch and the mean of the oscilating deviations immediately before the twitch were not within $\pm$ 10% of each other.

Lack of Reproducibility in the Transdiaphragmatic Pressure Twitch Amplitude Across Time and Within Subjects

In some of the subjects there was significant deviation in the amplitude of twitches during the experimental test day. We determined that these deviations were not the result of diaphragm fatigue and were therefore, the result of poor reproducibility. It is possible that there was some human error in the application of the CMS, as slight changes in the location of the CMS would result in significant changes in the Pdi twitch amplitude. However, in attempt to overcome this, once the location in which the largest Pdi response was elicited the location was marked with a bright marker and the experimenter used that landmark for all future stimulations. It is also possible that this lack of reproducibility in the Pdi twitch amplitude is related to the lack of supramaximal stimulations in some of the subjects.

Effort Dependent Measurements

Some of the measurements done in this study such as the IC maneuvers and the MIP maneuvers were dependent on the effort given by the subject. These measures required that the subject perform a maximal effort in order to obtain real values. If the subject did not perform maximal efforts while performing these measures a lack of reproducibility would result. To overcome this, subjects were given specific instructions on how to perform these maneuvers and were familiarized with the procedures at rest and given ample time to practice on both testing days before moving on to the experimental measurements. Subjects were also given lots of encouragement when performing these measures in an attempt to elicit a truly maximal effort.

In order to determine if a true maximal effort was given on the IC maneuvers, the Poes was examined during the IC. Inspiratory capacity measures during the control exercise were not included in analysis if the Poes achieved during the IC was not equal to or greater than the Poes achieved during the IC maneuvers at rest. For the CWR exercise condition the IC was not included in analysis if the Poes was not within $\pm$ 10% of the other ICs performed in that condition.

If subjects did not perform maximal MIP maneuvers prior to the delivery of a potentiated twitch than the level of potentiation would be reduced which could result in an artificially decreased Pdi twitch amplitude. Only the last three, of the five MIPs that were performed in every set of potentiated twitches were included in analysis. This helped ensure the maximal amount of twitch potentiation was present in the twitches that were used in analysis.

Lack of Randomization in the Order of Condition

In this study both the control exercise condition and the CWR exercise condition were performed on the same day. Subsequently the order in which subjects underwent the exercise conditions was not randomized, and subjects always performed the control condition first followed by the CWR condition. This could have introduced some bias into the data. Subjects may also have shown general fatigue by the time the CWR condition had commenced or had been completed as the test day was extensive and lasted more then six hours. The order in which subjects underwent each condition was not randomized based on the assumption that subjects would not show diaphragm fatigue after ten minutes of exercise at 45% of VO_{2MAX}. One subjects showed a 17% drop in his potentiated twich Pdi amplitude 10 minutes after control exercise, however, his twitch Pdi amplitude had returned to baseline after 30 minutes. The assumption was made that all ventilatory, metabolic and pressure measures would return to baseline after the control exercise within 30 minutes. This may have been problematic as ensuring subjects had returned to baseline was challenging and relied on the experimenter. The criteria used to determine if subjects had returned to baseline were 1) that the Pdi twitch amplitude had returned to or exceeded baseline measures. 2) That the subject had returned to baseline in all ventilatory and metabolic parameters. Given this experimental design it is possible that some subjects may not have returned to baseline in their ventilatory or metabolic parameters, such as $PetCO_2$. However, it is suggested that the subjects were at baseline levels of $PetCO_2$ prior to the onset of CWR exercise as there was no difference in the $PetCO_2$ between the two conditions.

Conclusion

The purpose of this study was to examine the relationship between low intensity exercise with CWR and diaphragm fatigue. Diaphragm fatigue was shown to occur after low intensity exercise when the chest wall was restricted. A significantly higher work of breathing, reductions in resting lung volumes and operational lung volumes, and changes in the breathing patterns during exercise with CWR were also shown. Furthermore, these changes in the breathing mechanics replicated those see in restrictive disorders and may have been responsible for the observed diaphragm fatigue. A high negative linear correlation between I(el) and the percent drop in Pdi from baseline was found in this study suggesting that the degree of diaphragm fatigue is greatly related to a high I(el). The results from this study indicate that CWR may be a good model of restrictive disorders and that it is possible

to fatigue the diaphragm when exercising at low intensities when the compliance of the chest wall is reduced due to CWR.

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APPENDIX A
REVIEW OF LITERATURE

Chest Wall Restriction

Chest wall restriction (CWR) is a technique, which involves physically restricting the chest wall causing a reduction in the compliance of the thoracic wall and consequently altering the mechanics of the breathing cycle. Altering the breathing mechanics with CWR elicits a reduction in resting lung volumes and induces a rapid, shallow breathing pattern (Harty et al., 1999; Miller et al., 2002; O'Donnell et al., 2000). Upon inhalation the chest wall expands allowing the lungs to increase in volume and fill with air. However, when the chest wall is restricted one's ability to expand their thoracic cavity is limited (Cline et al., 1999; Coast and Cline 2004). Furthermore, due to the reduced compliance of the chest wall subjects have a significantly higher work of breathing and experience exertional dyspnea leading to decreased exercise tolerance compared to control subjects (Miller et al., 2002; O'Donnell et al., 2000).

The breathing mechanics elicited by imposing chest wall restriction are similar to many restrictive lung diseases and deformities of the chest wall such as; kyphoscoliosis, pectus excatvatum, ankylosing spondlitis, pleural disease, neuromuscular disease, abdominal distention, chest wall paralysis, interstitial lung disease and obesity (Cline et al., 1999; Coast and Cline, 2004; Miller et al., 2002; O'Donnell et al., 2000). As well, CWR occurs in certain occupational settings, such as policing when body armour or bulletproof vests are required (Cline et al., 1999; Coast and Cline, 2004). Individuals with restrictive lung disease, similar to CWR healthy subjects suffer from significant reductions in chest wall compliance, resting lung volumes, pulmonary function and exercise intolerance (Cline et al., 1999; O'Donnell et al., 2000). The breathing pattern, which characterizes restrictive lung disease involves, a high tidal volume (V_T) to inspiratory capacity (IC) ratio and relative tachypnea at low exercise intensities. For the purposes of this review, comparisons in chest wall compliance, breathing mechanics and diaphragm fatigue will be made between healthy humans, CWR healthy subjects and restrictive lung diseases in order to strengthen the use of CWR in healthy subjects as a model of restrictive lung diseases. CWR in healthy subjects will be discussed in relation to its affects on resting lung volumes, breathing mechanics, compliance, the work of breathing and diaphragm fatigue. Anatomical characteristics of the diaphragm and how they relate to fatigue will also be discussed.

Individuals with restrictive lung disease not only experience difficulties in ventilation, but may also have a blunted cardiac output response during exercise, which could contribute to their exercise intolerance (Eliot et al. 1985). This is not, however, a universal finding (Kowalewski et al., 1999; Zhao et al., 2000). Elliot et al. (1985), found that subjects with ankyloid spondylitis had decreased performance on a ramp exercise test and that their reduced oxygen consumption (VO_{2MAX}) was due to cardiovascular limitations and not ventilatory limitations. Zhao et al., (2000) examined cardiac filling in subjects with pectus excavatum and found that in a sitting position these subjects had a reduced VO_{2MAX} and stroke volume, but in a supine position these measures were close to those of a normal subject. The authors suggest that the reduced VO_{2MAX} and stroke volume of pectus excavatum patients in the sitting position is the result of compression on the right heart chambers by the displaced sternum. This limits the expansion of stroke volume during exercise. They do however, report forced vital capacities (FVC) of 70 $\pm$ 15% in the sitting position and 63 $\pm$ 13% in the supine position, of their subjects predicted FVC. As well, these subjects have reduced total lung capacities (TLC) at 85 $\pm$ 12 % of their predicted TLC (Zhao et al., 2000). Patients with congestive heart failure have been shown to have abnormal cardiorespiratory interactions due to an increase in cardiac size, altered pulmonary and intrathoracic pressures, increased intrathoracic fluid and an elevated work of breathing (Mancini, 1995). Historically it was believed that the exercise intolerance in congestive heart failure was due to dysfunction of the heart. However, the degree of alteration in lung mechanics and enhanced cardiorespiratory interactions in congestive heart failure patients is still unknown and could contribute to exercise limitations (Mancini, 1995). Furthermore, individuals with congestive heart failure have a more tachypneic breathing pattern, breath at lower lung volumes, and suffer from significant expiratory flow limitation (EFL), when compared to normal healthy controls (Johnson et al., 2000).

Respiratory Drive in Restrictive Lung Disease

Sensations of dyspnea are a main limiting factor to exercise performance and are often experienced by patients with restrictive lung disease at relatively low levels of exercise (Harty et al., 1999; O'Donnell et al., 2000). These patients may suffer from excessive stimulation of pulmonary receptors secondary to interstitial inflammation, fibrosis, or the collapse of alveoli at low lung volumes (Harty et al., 1999). There may also be altered afferent information from fusimotor muscle spindles in the intercostals, golgi tendon organs, or joint receptors in the rib cage due to the decreased

V_T and low thoracic volumes (Harty et al., 1999). The combination of these factors could potentially lead to an enhanced respiratory drive. In a study examining CWR and dyspnea, O'Donnell et al., (2000) postulated that feelings of dyspnea might be enhanced in people who, at rest have a mechanical restriction of their chest wall (people with restrictive lung disease) and a reduced mechanical response to an excessive respiratory drive. In this population dyspnea may be further augmented due to alterations in gas exchange and an enhanced sense of effort, which accompanies an increase in mechanical load (Harty et al., 1999). The presence of mechanical restriction and increased respiratory drive during exercise may increase ventilatory limitations and hasten the onset of intolerable dyspnea which together limit exercise capacity (O'Donnell et al., 2000). In a disease state however, it is difficult to evaluate the relative importance of mechanical restriction and enhanced ventilatory demand on how these factors are interrelated and contribute to the development of dyspnea and exercise intolerance (O'Donnell et al., 2000). For these reasons it is important to find a model of restrictive lung disease, which can be employed to closely examine these factors.

External Restriction of the Chest Wall

The use of external devices to manually restrict the chest wall, has been used as a model of restrictive lung disease at rest and during exercise. CWR has been shown to reduce exercise capacity by 20-30% in healthy people and CWR has been able to produce significant reductions in resting lung volumes and similar breathing patterns to those observed in individuals with restrictive lung disease (Miller et al., 2002). Using CWR to decrease a subject's ability to expand their chest wall results in reductions in inspiratory volume (Cline et al., 1999).

Resting Lung Volumes in Chest Wall Restriction

In 2002, Miller et al. examined the breathing mechanics and breathing patterns of CWR subjects. They found that using inelastic straps to restrict the chest wall resulted in an average 33% reduction in total lung capacity (TLC) and an average 38% reduction in vital capacity (VC). They also found that residual volume (RV) was reduced by 23%. In a similar study by O'Donnell et al., (2000) they found a 35 $\pm$ 2% reduction in FVC primarily due to a decrease in TLC. A reduction in RV was not found, however, a 36 $\pm$ 2% reduction in IC resulted due to reductions in TLC and functional residual capacity (FRC). This decrease in IC resulted in a further 45 $\pm$ 2% decrease in inspiratory reserve volume (IRV) (see appendix C for figures displaying MFVL from Miller et al.,

2002 and O'Donnell et al., 2000). The reductions in IC and IRV cause a mechanical constraint on V_T during exercise and result in a significantly more rapid and shallow breathing pattern (O'Donnell et al., 2000). The significant reductions in TLC and the minimal reduction in RV are typical of restrictive lung diseases while significant increases in TLC and RV are characteristic of obstructive diseases (Mancini et al., 1995). Furthermore, exercise capacity was reduced and peak work during exercise fell 15 $\pm$ 1% while total accumulative work during exercise fell 28 $\pm$ 3% in CWR subjects (O'Donnell et al., 2000).

Breathing Mechanics

Breathing mechanics in CWR subjects are altered due to reductions in chest wall compliance. However, it is important to review breathing mechanics in normal healthy individuals in the absence of CWR before reviewing the breathing mechanics in CWR individuals.

Breathing Cycle

In normal healthy unrestricted subjects, contractions of the diaphragm result in an expansion of the thoracic cavity, a caudal displacement of the abdominal viscera and an increase in gastric pressure (Pga). Simultaneously, the ribs are lifted up and outward by the external intercostals, resulting in a further increase in volume of the thoracic cavity and a decrease in intrapleural pressure (Ppl) (from –5 cmH_2O to –10 cmH_2O) (Banner, 1995). The drop in Ppl during inspiration is due to the increase in elastic recoil of the lungs as the thoracic cavity expands and the pressures along the airways drop (West, 2000). Due to the contraction of the inspiratory muscles and the resulting increase in volume of the thoracic cavity, the volume of the alveoli increases. The increased volume of the alveoli results in a decrease in alveolar pressure below atmospheric (0 cmH_2O). During breathing at rest, alveolar pressure drops from 0 cm H_20 to – 1 cm H_20, allowing inspiration to occur. This allows for air to travel down the pressure gradient and into the alveoli. The flow of air into the alveoli continues until the elastic recoil forces of the lungs offset the force produced by the inspiratory muscles. At this point the pressure in the alveoli returns to atmospheric (0 cmH_2O), inspiration ends and the inspiratory muscles relax. Due to the recoil forces of the lungs at this point the pressure in the alveoli exceeds atmospheric at about 1 cmH_2O and expiratory flow begins. Expiratory flow continues until the pressure in the alveoli is equal to atmospheric and the recoil pressures of the respiratory system are zero, this is referred to as the functional residual capacity

(FRC) (West, 2000). The breathing cycle, breathing mechanics and pressures generated during the breathing cycle are different in CWR subjects compared to unrestricted controls due to reduced compliance of the chest wall.

The pressure across the diaphragm, referred to as the transdiaphragmatic pressure (Pdi), is the difference between gastric pressure (Pga) and intrapleural pressure (Ppl), (Pdi = Pga – Ppl) and is used to assess the force generated during a contraction of the diaphragm (Banner, 1995). Gastric pressure is measured with a balloon tipped catheter placed in the stomach while intrapleural pressure is measured indirectly using a balloon tipped catheter placed in the esophagus. During quiet inspiration, transdiaphragmatic pressure increases by about 10 cmH_2O, however, it may reach maximal values up to 100-150 cmH_2O during exercise or if the work of breathing is increased such as in certain disease conditions (Banner, 1995). Due to the decreased compliance of the chest wall, CWR subjects or individuals with restricted lung disease require a much larger Pdi to generate inspiration, resulting in an increased work of breathing. The pressure production of the diaphragm is evaluated using the time integrals of Pdi ($\int Pdi*f$) and the total work of the respiratory system can be evaluated by changes in the time integral of Ppl ($\int Ppl*f$). Statistically significant differences between CWR subjects and unrestricted controls for $\int$ Pga time integrals and $\int$ Pdi time integrals, at rest and during exercise at an intensity of 45% of VO_{2MAX} have been demonstrated (Miller et al., 2002). For CWR subjects the $\int$ Pga time integrals averaged 751 $\pm$ 421 cmH_2O*s compared to control subjects, who had an average $\int$ Pga time integral of 140 $\pm$ 72 cmH_2O*s. Also at rest they found $\int$ Pdi time integral of 866 $\pm$ 474 cmH_2O*s in CWR subjects compared to 247 $\pm$ 71 cmH_2O*s in control subjects. Furthermore, at 45% of VO_{2MAX} they found an average $\int$ Pga time integral of 1097 $\pm$ 213 cmH_2O*s in CWR subjects compared to 178 $\pm$ 57 cmH_2O*s in control subjects and an average $\int$ Pdi time integral of 1441 $\pm$ 76 cmH_2O*s was found in CWR subjects while 371 $\pm$ 56 cmH_2O*s was found in control subjects (Miller et al., 2002).

The maximal flow volume loops (MFVL) generated by CWR subjects are much smaller than those generated by unrestricted healthy control subjects (Miller et al., 2002). This is due to the physical restriction and reduced compliance of the chest wall. Therefore, CWR subjects have significantly smaller FVC. Maximal flow volume loops are generated when a person performs a maximal inspiration followed by a maximal expiration. From the MFVL the FVC, forced expiratory volume in one second (FEV_1), the ratio of FEV_1/FVC and peak expiratory flow rate are determined (Barreiro TJ and Perillo I, 2004). These values are often used to diagnose respiratory disorders

including restrictive lung disease. In individuals with restrictive lung disease, FVC is significantly reduced from their predicted value, based on age, sex, height and weight. A reduction in FEV_1 will also be present in restrictive lung disease but it will be in proportion to FVC; therefore the FEV_1/FVC ratio will be normal (Barreiro TJ and Perillo I, 2004).

Compliance

Changes in breathing mechanics present in CWR subjects are largely due to reductions in compliance of the chest wall and the resulting reduction in compliance of the respiratory system. It is necessary to understand how compliance of the chest wall and the lung work in isolation and in combination in order to understand the change in compliance that occurs in CWR.

Compliance of the Lung

The lungs have a tendency to collapse inward while the chest wall has a tendency to spring outward. When in isolation, the lungs are at a much smaller volume, below RV and the chest wall is at a much larger volume, approximately 55% of VC. Therefore, the intact respiratory system (the combination of the chest wall and lungs together) works to balance out the collapsing forces of the lungs and the expanding forces of the chest wall. The volume of air in the lungs when the respiratory system is at rest is the FRC which is a greater than the lungs in isolation and a smaller than thoracic cavity in isolation (Comoroe et al., 1962).

Compliance is defined as the change in volume per unit change in pressure (Comoroe et al., 1962; Halstala and Berger, 1996; West, 2000) (see appendix Figure 1). Expansion of the thorax results in an increase in the volume of the thoracic cavity with a corresponding drop in intrapleural pressure below atmospheric allowing air to enter into the lung. In order to measure compliance accurately the resistance to flow must be eliminated (Grinnan and Truwit, 2005), therefore, if lung volume is frozen in time and pressure is held constant, volume can be measured and a plotted against pressure to produce a pressure-volume curve. The slope of the pressure-volume curve is compliance (West, 2000). The pressures needed to generate certain volume changes on inhalation are larger than on exhalation due to the increased effort required to separate the walls of fully closed alveoli. This physiological phenomenon is termed hysteresis (West, 2000). At normal intrapleural pressures (from -2 to -10 cmH_2O), the lung is very compliant and the curve is close to a straight line with a slope of

200ml/cmH_2O (West, 2000). Nonetheless, as higher expanding pressures are reached (the flatter portion of the pressure-volume curve) the lung becomes stiffer and less compliant.

The compliance of the lung is determined by two main factors: 1) the elasticicty of the lung and 2) the surface tension of the fluid lining the alveoli (West, 2000). The lung is made up of both elastin and collagen fibers, which are located in the alveolar walls and around vessels and bronchi. The elastic properties of the lung, which have the opposite action of compliance, cause the lungs to recoil, following distension (West, 2000).

Compliance of the Chest Wall

The pressure volume curve of the chest wall has a different shape to that of the lung, due to the tendency of the chest wall to spring outward (West, 2000). The pressure volume curve of the chest wall flattens at low lung volumes as the chest wall reaches its collapsible limit. During breathing at rest in healthy humans, (with intrapleural pressures between –2 and -10cmH_2O), the pressure-volume curve approximates a straight line and is almost equal to lung compliance.

The compliance of the chest wall is determined by two main factors; 1) The elasticity of the tissues of the chest wall and 2) the elasticity of the external pressures applied to the chest wall (Smith and Loring, 1986). In healthy individuals the elasticity of the chest wall remains relatively unchanged until advance age, however; in obesity or certain disease conditions it may be affected. The elasticity of external pressures applied to the chest wall may be altered in situations where an external restrictive device is applied to the chest, during emersion in water and during postural changes. For example, moving from an upright to supine position causes the weight of the abdominal contents to sit against the diaphragm. In these situations compliance of the thoracic wall is not changed but the resting volume of the thoracic space is changed (Smith and Loring, 1986). It is the elasticity of the external pressures applied to the chest wall, which are affected in CWR subjects, as an inelastic external pressure is placed around the chest wall

The elastic properties of the chest wall can be demonstrated using a pneumothorax. If there is a puncture in one of the lungs, the lung collapses inwards while the chest wall springs outwards. In a state of equilibrium the chest wall pulls the lungs outwards and the chest wall is pulled inwards by the lungs resulting in a balance at FRC. It is at FRC where the outward recoil force of the chest wall is precisely offset by the inward positive recoil force of the lungs and the pressures required to inflate the lungs and deflate the thoracic cage are equal (West, 2000). At FRC the inspiratory muscles must

reduce the intrapleural pressure by expanding the thoracic space allowing for inspiration to occur. The pressure-volume curve of the lung and chest wall together depicts the pressure required to generate specific changes in volume of the respiratory system. At any volume the slope of the pressure-volume curve for the entire respiratory system is less than the slope of the pressure-volume curve of either the chest wall or lung in isolation. Furthermore, greater pressures are required to distend the chest wall and lungs together than either separately (Hlastala and Berger, 1996). Pressure is inversely proportional to compliance, implying that total compliance of the lung and chest wall is the sum of the reciprocals of lung and chest wall compliance ($1/C_{TOT} = 1/C_l + 1/C_{cw}$) (West, 2000).

In conditions like congestive heart failure where there is edema in the lungs, lung compliance is reduced due to the inability to inflate some of the alveoli. FRC is also reduced due to the enlargement of the heart, pleural or pericardial effusions and ascites. In certain disease conditions reductions in compliance are accompanied by reductions in FRC (Comoroe et al., 1962). Reductions in lung compliance occur in conditions, which involve fibrosis, while increases in lung compliance occur as part of the natural aging process and in chronic obstructive pulmonary disease (West, 2000).

Breathing Patterns

Breathing patterns involve a combination of V_T and breathing frequency. In normal, healthy humans V_T is approximately 500 mL during rest. V_T increases as exercise intensity rises and higher ventilation rates are required. V_T increases steadily up to about 60% of VC. At this point V_T plateaus and further increases in V_E are the result of increases in breathing frequency (West, 2000). Chest wall restriction induces a change in this breathing pattern; V_T is decreased at rest and cannot be significantly increased during exercise due to the reductions in IRV. During exercise this leads to significantly greater breathing frequencies with minimal enlargements in V_T. Small increases in minute ventilation and the ventilatory equivalent of CO_2 (V_E/VCO_2) result from this breathing pattern (Miller et al., 2002). This phenomenon has been shown to occur even at low exercise intensities (25% and 45% of VO_{2MAX}) (Miller et al, 2002) and is the breathing pattern present during exercise in individuals with restrictive lung disease (Johnson et al., 2000; Mancini 1995; O'Donnell et al., 2000). Furthermore, it is this rapid, shallow breathing pattern that leads to enhanced sensations of dyspnea during exercise and may play a role in exercise intolerance (O'Donnell et al., 2000). Despite the significantly reduced V_T, V_E is essentially the same as in unrestricted healthy humans. Furthermore, tidal expiratory flow rates in healthy unrestricted individuals exercising at low intensities (25-45% of

VO_{2MAX}) do not approach their maximal expiratory flow rates, however, the tidal expiratory flow rates in CWR subjects exercising at the same intensities do approach their maximal expiratory flow rates and EFL may occur (Miller et al., 2002).

In healthy unrestricted control subjects, increasing exercise intensity activates the expiratory muscles resulting in a reduction of the end expiratory lung volume (EELV). This reduction in EELV aids the inspiratory muscles by putting the diaphragm in a lengthened position, which is optimal for force generation. Increases in V_T are also achieved by an encroachment on both the inspiratory and expiratory reserve volumes. Furthermore, lung volumes are changing over the most linear and mechanically efficient part of the pressure-volume curve (Romer and Polkey, 2008, Dempsey et al., 2006). Elastic energy is also stored in the chest and abdominal walls during expiration and this stored energy may be used during inspiration (Romer and Polkey, 2008). However, in CWR subjects EELV is reduced at rest and during exercise at 25% of VO_{2MAX}, however, during exercise at 45% VO_{2MAX} there is an upward shift in EELV allowing subjects to access higher flow rates, which prevents EFL (Miller et al., 2002). While diaphragm is a highly fatigue resistant muscle there are times, such as, during high intensity exercise, when diaphragmatic contractions produce greater force or are longer in duration, which may result in fatigue. Lengthened contraction times of the diaphragm are illustrated as changes in duty cycle.

Duty Cycle

Contraction time of the diaphragm can be expressed in the duty cycle. Duty cycle is the ratio of inspiratory time T_I to the total respiratory time (T_{TOT}) (T_I/T_{TOT}). This represents the duration of diaphragmatic contraction over the total duration of the respiratory cycle. Under normal conditions the duty cycle is approximately 0.33, thus the inspiratory time is approximately one third of the total respiratory time. As this ratio becomes larger, either recovery time is reduced or the duration of diaphragm contractions are lengthened. During exercise larger force productions and durations of diaphragm contractions result due to an increased discharge firing frequency from the central nervous system, as well as an increased excitation from the central respiratory controllers, this results in a larger duty cycle (Banner, 1995). Bellemare and Grassino (1982) examined the relationship between the mean Pdi swing on inspiration and duty cycle. Subjects performed voluntary breathing tasks, utilizing different breathing patterns for 45 minutes or until Pdi could no longer be maintained. The specific breathing patterns they examined included, 15-90% of maximum Pdi and a duty cycle of

0.15-1.0. The work done by the diaphragm during these breathing tasks was then calculated as the tension time index of the diaphragm (TTdi = Pdi * T_I/T_{TOT}). They found that the critical Pdi value, (the Pdi value in which the breathing pattern can be maintained for greater than 45 minutes) was dependent on the duty cycle. Thus the duty cycle and Pdi values are inversely related. Roussos and Macklem found that normal subjects have a Pdicrit of 0.4 (40% of maximum Pdi) while breathing at a duty cycle of about 0.5 this equates to a TTdi of about 0.2. Bellmare and Grassino (1982), found that when a larger range of duty cylces were used the Pdicrit varied between 0.2 and 0.8 of maximum Pdi. This range in Pdi can be found in normal subjects breathing against a resistance or in individuals with COPD. The breathing pattern that could be maintained for greater than 45 minutes was represented by a TTdi of 0.15 and has been termed the critical TTdi (Bellemare and Grassino, 1982). The TTdi for subjects breathing room air at rest is 0.02 and therefore there is a large reserve available before the critical TTdi is reached.

Diaphragm Anatomical Characteristics

The diaphragm is an endurance-oriented muscle, which contracts repeatedly for the entire duration of one's life. It has a high oxidative capacity, short capillary to mitochondrial diffusion distance and an extensive blood supply making it one of the most fatigue resistant skeletal muscles in the body (Romer and Polkey, 2008; Dempsey et al., 2006). The diaphragm is a dome shaped skeletal muscle; it is the primary muscle responsible for inspiration and is one of the most fatigue resistant skeletal muscles in the human body. The diaphragm attaches to the xiphoid process, ribs 7-12, and the first 2 or 3 lumbar vertebra (Banner, 1995). The diaphragm is served by the phrenic nerve, which is composed of branches off C3- C5 nerve roots. During rest, contraction of the diaphragm accounts for 70% of the V_T in normal healthy humans (Banner, 1995). The external intercostals, scalene, and parasternal muscles make up the remaining 30% of the V_T as they elevate the rib cage and pull it forward during inspiration. As well, due to the repetitive nature of the breathing cycle, the diaphragm and other muscles of respiration are endurance-oriented muscles (Banner, 1995).

The composition of muscle fibers in the diaphragm reflects its primarily aerobic nature. The diaphragm is predominately (approximately 60%) composed of type I slow oxidative muscle fibers. Type IIA fast oxidative muscle fibers and type IIB fast glycolytic muscle fibers are also present but to a smaller extent (each is approximately 20%). Type I and type IIA muscle fibers have high concentrations of myoglobin, mitochondria, oxidative enzymes and capillary contents. Type I muscle

fibers are fatigue resistant and type IIA muscle fibers are moderately fatigue resistant while Type IIB muscle fibers lack myoglobin and fatigue rapidly (Banner, 1995). Despite the composition of the muscle fibers of the diaphragm, fatigue can occur in a few minutes when the duration or velocity of contractions is increased, such as during exercise (Banner, 1995).

The diaphragm is composed of two sections, the costal section and the crural section. The costal section, also known as the zone of apposition, forms the sides of the diaphragm and is the site where contraction occurs (West, 2000). The zone of apposition covers a significant portion of the rib cage surface, the degree to which is dependent on the length of the muscle fibers. At RV, when the length of muscle fibers are at their longest the zone of apposition covers about one half the surface of the rib cage. As the length of muscle fibers shorten and the zone of apposition is decreased an increasingly smaller portion of the rib cage is covered (Smith and Loring, 1986). When the costal fibers contract they pull on the crural section and the diaphragm flattens caudally. Under resting conditions the diaphragm is normally displaced about 1cm in healthy individuals (West, 2000). In forced inspiration the diaphragm may descend about 10cm (West, 2000).

Work of Breathing

In a fluid system, work is performed when a change in pressure results in a change in volume (Roussos and Campbell, 1986). The work of breathing can be assessed by integrating the area under the pressure -volume curve (Work of Breathing = $\int P\, dV$), (Banner, 1995). The physiological work of breathing is a combination of the elastic (Wel) and flow resistive work of breathing (Wfr) (total work = Wel + Wfr) (Roussos and Campbell, 1986). Elastic work of breathing is the work required to overcome the elastic forces of the respiratory system and flow resistive work is the work required to overcome the resistance to flow (Banner, 1995). When airway resistance is high as in certain disease conditions greater intrapleural pressure is required to generate inspiration (West, 2000).

At rest the work of breathing is minimal and relatively efficient at approximately 5% of the total VO_2. During voluntary hyperventilation this increases to about 30% of VO_2 (Hlastala and Berger, 1996). In high intensity exercise the oxygen cost of the inspiratory and expiratory muscles is approximately 8-10% of the total VO_2 (Aaron et al., 1992). However, the O_2 cost of breathing in highly fit subjects has been shown to be as high as 16% of total VO_2 (Harms et al., 1998). The discrepancy between the VO_2 cost during hyperventilation and during exercise is the result of a greater percentage of total VO_2 being available for the respiratory muscles during voluntary

hyperventilation compared to during high intensity exercise. During high intensity exercise a competition for blood flow between the respiratory muscles and the locomotor muscles ensues, resulting in a smaller percentage of VO_2 being available for the respiratory muscles.

The work of breathing is equal to $\int PdV$ and therefore, when a greater change in pressure is required to produce the same change in volume, the work of breathing increases. The work associated with breathing is also dependent on the length of the muscle fibers of the diaphragm, when the diaphragm is at its optimal length (FRC) little work is required to produce inhalation. However, when the muscle fibers are not at an optimal length the work of breathing will increase because the diaphragm must overcome its fiber length disparity to produce the same changes in volume. Patients suffering from obstructive lung diseases breathe at a higher FRC to reduce the flow resistive work. Patients suffering from restrictive lung diseases breath at lower FRC in order to reduce the elastic work of breathing, however, this comes at the cost of a higher flow resistive work of breathing (Hlastala and Berger, 1996). Both of these patient groups are breathing at volumes in which the diaphragm is not at its optimal length and therefore, the work of breathing for these individuals is greater than in healthy people breathing at FRC (Smith and Loring 1986 and West 2000).

In CWR the work of breathing is greater due to reductions in chest wall compliance. The respiratory muscles must generate greater pressures in order to overcome the elastic recoil forces of the lungs and produce inspiration. The $Pdi*f$ has been used as an indicator of how hard the diaphragm is working to produce inspiration. As Pdi is the difference between Pga and Poes, changes in either of these pressures will result in changes in the $\int Pdi*f$. It has been shown that the production of Pga in CWR subjects is significantly elevated compared to unrestricted subjects during exercise. This increased Pga in CWR subjects resulted in a greater increase in Pdi-time integrals in CWR subjects compared to unrestricted control subjects exercising at 45% of VO_{2MAX} (Miller et al., 2002). Despite the significantly greater Pdi present in CWR subjets the Wel was significantly reduced, at the expense of a significant increase in Wfr. However, like people with restrictive lung disease CWR subjects are breathing at a reduced EELV and therefore, it is not surprising that they would experience the same changes in the work of breathing. Therefore the total work of breathing was slightly increased (Miller et al., 2002). Despite the minimal increase in the total work of the respiratory system in CWR subjects it is evident that the diaphragm is working significantly harder due to the significantly greater $\int Pdi*f$ in CWR subjects compared to controls. Due to this significantly

increased muscular work of the diaphragm it is possible that fatigue may occur at lower intensities of exercise in the CWR condition compared to unrestricted exercise.

Diaphragm Fatigue

Muscle fatigue is defined, as "a condition in which there is a loss in the capacity for developing force and/or velocity of a muscle, resulting from muscular activity under a load and which is reversible by rest" (Romer and Polkey, 2008, National Heart Lung and Blood Institute Workshop, 1990). There are three types of diaphragm fatigue, which may occur during or after high intensity exercise, central fatigue, peripheral high-frequency fatigue and peripheral low-frequency fatigue (American Thoracic Society/European Respiratory Society, 2002).

Central fatigue occurs due to declining motoneuronal output from the central nervous system, which leads to a corresponding decline in diaphragm contractions (American Thoracic Society/European Respiratory Society, 2002). Both low- and high-frequency peripheral fatigue occurs when there is a failure at the neuromuscular junction, resulting in decreased motor force output or velocity in response to direct electrical or magnetic stimuli (American Thoracic Society/European Respiratory Society, 2002).

High-frequency peripheral fatigue is associated with a loss of force after stimulation at high frequencies (50-100Hz), which is accompanied by a loss of amplitude and a slowing of the waveform of the muscle action potential. High frequency fatigue is characterized by the following features 1) there is a loss of force after stimulations at high frequencies and is quickly reversed by reducing the stimulation frequency. 2) Force loss is accompanied by a decrease in amplitude and the slowing of the waveform of a muscle action potential. 3) The loss of force is augmented if there is a loss in extracellular [Na^+] and an increase in extracellular [K^+] (Adrich et al., 1988; Jones 1996). However, it has been suggested that high frequency fatigue is not important to human performance as the stimulation frequency required to produced high frequency fatigue is much greater than the frequency at which motor units fire naturally (Jones 1996).

Low frequency fatigue persists despite an absence of gross metabolic or electrical stimulation of the muscle (Aldrich et al., 1988). Low frequency fatigue may be the consequence of structural damage to the muscle fibers and/or damage to the excitation-contraction coupling mechanism. This theory of fatigue is strengthened by evidence showing that low frequency fatigue occurs most readily when the muscle is stretched or when the muscles is worked isometrically at long lengths, as these

types of exercise can cause severe damage to muscle fibers. The slow recovery from low frequency fatigue may be due to the necessity to repair the muscle, which is reliant on protein turnover and not metabolite resynthesis (Jones1996). It has also been suggested that low-frequency fatigue may be related to a drop in calcium release during the action potential or a decrease in the calcium sensitivity of troponin (Jones, 1996).

Even though the diaphragm is an endurance-oriented muscle it is capable of experiencing fatigue in a variety of scenarios including; high intensity exercise sustained till exhaustion, respiratory muscle loading and in certain disease conditions. The clinical manifestation of respiratory muscle fatigue occurs in the following sequence: 1) An increase in breathing frequency, followed by 2) The development of discoordinated respiratory movement termed the abdominal paradox, (abdomen displaces inward upon inspiration), 3) an increase in $PaCO_2$ and respiratory academia and finally 4) a terminal decrease in respiratory rate and minute ventilation (Banner, 1995). As the respiratory muscles become fatigued afferent information from pulmonary receptors located in the airways and respiratory muscles is directed back to the central respiratory centers to modify the breathing pattern. To minimize respiratory muscle fatigue, increases in intrapleural pressure occur and the respiratory center increases the breathing frequency minimizing the contraction time of the diaphragm (Banner, 1995). This results in a decreased tidal volume and a rapid, shallow breathing pattern. Spontaneous breathing frequency has been used as an inference of the work of breathing by clinicians. A breathing frequency greater than 25-30 breaths per minute (bpm) indicates an abnormally high work of breathing. A tolerable work of breathing is inferred at a breathing frequency of approximately 15-20 bpm (Banner, 1995).

Exercise induced diaphragm fatigue has been studied extensively and has been shown to occur in healthy humans exercising at intensities of 80-85% of VO_{2MAX} sustained till volitional fatigue (Babcock et al., 1995; Dempsey et al., 2006; Johnson et al., 1993; Romer and Polkey, 2008) or if oxygen saturation (SaO_2) drops below ~85% (Babcock et al., 1995; Romer and Polkey, 2008).

Evidence for the Combination of a High Work of Breathing and High Intensity Exercise

The work of breathing has been linked to the development of diaphragm fatigue in studies, which illustrate that diaphragm fatigue does not occur when the work of breathing is unloaded (Babcock et al., 2002). Nonetheless, the use of mimic trials has provided evidence to suggest that a high work of breathing in isolation is not sufficient to induce diaphragm fatigue (Babcock et al.,

1995). Babcock et al., (1995) investigated healthy humans while they mimicked the breathing patterns and pressures present in high intensity exercise known to cause fatigue. These subjects did not experience diaphragm fatigue when mimicking these breathing patterns suggesting that a high work of breathing alone is not sufficient to cause diaphragm fatigue. It has been proposed that during high intensity exercise a competition for blood flow ensues between the working locomotor muscles and the diaphragm. Therefore, it is possible that it is the combination of a competition for blood flow in the presence of a high work of breathing which leads to diaphragm fatigue (Dempsey et al., 2006). In CWR subjects, it is possible that the work of breathing is so significantly elevated that diaphragm fatigue will occur at substantially lower exercise intensities.

Respiratory Muscle Recruitment

The relative contribution of the diaphragm to total ventilation may change over the course of exercise. Exercise performance may be affected as the relative contribution of the diaphragm to total V_T is reduced, when exercise intensity increases or as diaphragm fatigue occurs (Romer and Polkey, 2008). The differences in diaphragm fatigue between highly fit individuals and averagely fit individuals has been examined and shown that in a group of highly-fit individuals greater diaphragmatic force was produced during the first 60% of the exercise time compared to in a group of fit individuals. In the last 40-50% of the exercise bout however, the two groups produced a comparable amount of diaphragmatic force. It was suggested, that higher ventilation rates achieved by the high fit group later in exercise were therefore, dependent on the recruitment of accessory inspiratory muscles (Babcock et al., 1996). Furthermore, the introduction of accessory inspiratory muscles and expiratory muscles may be necessary to enable the progressive hyperventilatory response to exercise (Babcock et al., 1995; Babcock et al., 1996; Johnson et al., 1992; Romer and Polkey, 2008). The increased contribution of accessory muscle to inspiration may distort the chest wall and reduce the mechanical efficiency of breathing. This could result in an increase in the metabolic and blood flow demands of these muscles and may contribute to the presence of diaphragm fatigue. Sensations of dyspnea may also be enhanced as the recruitment of accessory muscles of inspiration may increase sensory input to the central nervous system (Romer and Polkey, 2008).

Increasing exercise intensity and ventilation rates, results in increasing compression of the airways due to the high pleural pressures during expiration. This increase in airway compression causes flow limitation to occur and may cause an increase in EELV. Increases in EELV enhance

expiratory flow by allowing the individual to breathe at higher lung volumes and access the higher flow rates available at these volumes (Klas and Dempsey, 1989). At higher lung volumes however, the inspiratory muscles have to work harder to overcome the greater elastic loads of the lungs and chest wall (Milic-Emili and Petit, 1960). Highly fit individuals exercising at VO_{2MAX} can increase their expiratory flow rates to levels, which exceed their maximal expiratory flow, making them flow limited (Johnson et al., 1992). To maintain their ventilatory needs the respiratory muscles require a large blood flow and O_2 supply. It has been shown that in highly fit individuals during maximal exercise, 10-15% of the total VO_{2MAX} or 300-600 ml/min of absolute VO_2 and 14-16% of the total cardiac output are used for the inspiratory and expiratory muscles (Aaron et al., 1992; Harms et al., 1998). This takes blood flow away from the locomotor muscles and a competition for blood flow between the locomotor muscles and the respiratory muscles ensues. Therefore, both a high work of breathing in the presence of high intensity exercise is necessary to induce fatigue in the diaphragm.

Blood Flow

Exercise induced diaphragm fatigue is the result of a high inspiratory muscle work that is sustained during high intensity exercise, as well as, a competition for blood flow between respiratory and locomotor muscles (Dempsey et al., 2006). Harms et al., (1997) studied blood flow to the legs while cycling when the work of breathing was reduced using PAV as well as when the respiratory muscles were loaded using a graded resistive load. It was found that decreasing the work of breathing resulted in a statistically significant increase in blood flow to the legs. Furthermore, adding a graded resistive load to the respiratory muscles resulted in a significant reduction in blood flow to the legs. A significant negative curvilinear relationship was found between the work of breathing and limb blood flow ($r = - 0.84$). As well, the ratio of VO_{2legs} to VO_{2TOT} increased from 81 $\pm$ 1% in the control condition to 89 $\pm$ 1% in the unloaded conditions and decreased to 71 = 1% in the loaded condition.

Diaphragm Fatigue During or After Exercise

In a study examining the onset time of diaphragm fatigue, changes in twitch Pdi before, during and after exercise were measured. It was found that the strength of diaphragmatic contractions increased progressively throughout exercise and significant diaphragm fatigue was only detectable after the termination of exercise. It was found that V_T, breathing frequency and V_E all increased during exercise. It was suggested that this could only be achieved by a corresponding

increases in respiratory muscle work (Kabitz et al., 2007a). These findings lead Kabitz et al., (2007b), to examine diaphragm force generation in high intensity exercise compared to voluntary hyperventilation. They hypothesized that ventilatory demands control diaphragm force production but that diaphragm fatigue develops independently from ventilatory demands. They found that diaphragm force production progressively increased throughout exercise and voluntary hyperventilation, and that both breathing regimes followed the same pattern of increase. They showed that diaphragm fatigue occurred after the exercise condition, however, diaphragm fatigue did not occur after the condition involving voluntary hyperventilation, and in fact diaphragm strength had increased. They concluded that force production of the diaphragm was similarly regulated by ventilatory demands rather than metabolic or circulatory demands during exercise and during voluntary hyperventilation, but not during recovery (Kabitz et al. 2007b).

Conclusion

During exercise in CWR subjects the work of breathing and specifically the work of the diaphragm, as indicated by large increases in the $\int Pdi*f$ is greater during exercise in unrestricted control subjects (Miller et al., 2002). Due to the large increases in the $\int Pdi*f$ in CWR subjects, it is suggested that diaphragm fatigue may occur at a much smaller percentage of VO_{2MAX}. Restriction in the magnitude of a 40% reduction in FVC may result in diaphragm fatigue at exercise intensities as low as 45%, for a fixed period of time in CWR subjects. To date there have been no studies examining the effects of CWR on diaphragm fatigue in healthy humans.

APPENDIX B
INDIVIDUAL DATA

Table 9. Individual breathing frequency, measured in breaths per minute (bpm), data for the control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	26.1	28.3	26.7	29.1	29.1
2	21.6	21.5	19.9	21.6	20.9
3	19.1	22.8	28.7	30.0	30.3
4		14.6	14.2	23.4	27.8
5	28.0	31.2	31.9	31.5	33.1
6	18.1	20.3	17.9	21.2	19.0
7	12.4	20.1	17.8	21.8	23.8

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	31.0	41.0	44.9	45.2	45.7
2	27.7	31.2	33.3	32.4	33.4
3	30.7	34.2	40.8	44.5	50.4
4	25.6	27.2	29.3	32.0	35.2
5	55.1	52.9	49.1	51.4	54.5
6	23.0	32.0	33.3	35.1	37.6
7	36.4	42.5	45.3	43.2	44.6

Table 10. Individual tidal volume, measured in liters (L), data for control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	2.10	2.11	2.10	1.97	1.94
2	2.46	2.99	3.08	3.02	3.05
3	2.32	2.14	1.83	1.79	1.78
4		3.45	3.40	2.52	2.09
5	1.83	2.23	2.23	2.17	2.07
6	1.32	2.06	2.09	2.11	2.01
7	3.62	3.84	3.95	3.54	3.15

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	1.37	1.46	1.46	1.54	1.38
2	1.56	1.88	1.92	2.04	2.10
3	1.81	1.61	1.51	1.41	1.33
4	2.02	1.96	1.97	1.91	1.83
5	1.29	1.51	1.45	1.45	1.47
6	1.23	1.49	1.45	1.43	1.41
7	1.99	1.78	1.59	1.80	1.72

Table 11. Individual ventilation data, measured in liters per minute (L/min), for control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	54.67	59.63	56.16	57.13	56.44
2	53.14	64.37	61.29	65.35	63.75
3	44.15	48.87	52.38	53.59	53.98
4		50.27	48.24	59.02	58.06
5	51.11	69.56	71.04	68.36	68.56
6	23.84	41.74	37.40	44.83	38.06
7	44.91	77.26	70.38	77.15	74.93

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	42.49	60.06	65.66	69.79	63.21
2	43.22	58.68	64.13	65.95	70.32
3	55.42	55.12	61.48	62.76	66.90
4	51.70	53.34	57.63	60.92	64.51
5	70.97	79.97	71.20	74.71	79.86
6	28.24	47.72	48.34	50.20	53.16
7	72.59	75.74	72.03	77.81	76.81

Table 12. Individual end tidal CO_2, measured in cmH_2O data for the control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	46.04	47.57	46.99	46.84	
2	47.82	46.76	46.73	47.78	46.73
3	53.48	50.58	49.47	48.67	48.67
4					
5	39.76	39.72	39.63	39.53	37.82
6					
7	46.31	45.49	46.43	43.43	43.56

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	42.28	45.98	45.78	47.19	
2	40.95	40.95	41.54	44.29	43.36
3	45.66	45.96	43.66	42.70	42.05
4	45.52	46.72	46.27	45.76	43.26
5	36.67	37.25	38.87	38.12	37.13
6	51.40	50.26	48.07	47.34	47.42
7	41.21	42.42	41.67	41.22	44.41

Table 13. Individual heart rate data, measured in beats per minute (bpm), for the control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	109	104	112	111	112
2	113	114	115	120	121
3	131	133	150	143	152
4	141	141	147	152	155
5	117	118	123	125	128
6	155	162	165	168	166
7	106	113	115	120	121

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	121	119	128	135	135
2	126	128	135	141	147
3	142	145	159	164	166
4	149	149	156	161	166
5	129	135	143	149	152
6	155	162	165	168	166
7	114	115	118	122	125

Table 14. Individual SaO_2 data, measured as a percentage (%), for the control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	97	98	97	96	95
2	97	97	98	96	96
3	97	97	98	96	96
4	99	98	98	98	98
5	96	97	97	97	96
6	95	97	96	95	94
7	98	98	98	98	98

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	94	94	92	92	92
2	91	96	95	96	96
3	98	97	97	97	96
4	97	98	96	95	96
5	92	95	95	95	95
6	94	92	88	87	88
7	92	95	93	94	95

Table 15. Individual leg discomfort ratings of perceived exertion for control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	3.0	3.0	3.0	3.0	3.0
2	1.0	1.0	2.0	2.0	2.0
3	3.0	4.0	4.0	4.0	4.0
4	1.0	2.0	2.0	2.0	2.0
5	3.0	3.0	3.0	3.0	3.0
6	3.0	3.5	4.0	4.0	4.0
7	2.0	2.0	2.0	2.0	2.0

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	2.5	3.0	3.0	3.0	3.0
2	1.0	1.0	1.0	1.0	1.0
3	3.0	3.0	3.0	3.0	4.0
4	1.0	2.0	2.0	2.0	2.0
5	2.0	2.0	2.0	2.0	2.0
6	3.0	3.0	4.0	5.0	5.0
7	2.0	2.0	2.0	2.0	2.0

Table 16. Individual dyspnea ratings (ratings of perceived exertion) for the control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	3.0	3.0	3.0	3.0	3.0
2	1.0	1.0	2.0	2.0	2.0
3	2.0	3.0	4.0	4.0	4.0
4	0.5	0.5	1.0	1.0	1.0
5	2.0	3.0	3.0	3.0	3.0
6	3.0	3.5	3.5	3.5	3.0
7	0.5	1.0	2.0	2.0	2.0

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	5.0	7.0	7.0	7.5	7.5
2	2.0	3.0	3.0	4.0	5.0
3	6.0	6.0	6.0	7.0	7.0
4	2.0	3.0	4.0	4.0	5.0
5	4.0	4.0	4.0	4.0	4.0
6	5.0	5.5	6.0	7.0	7.0
7	4.5	5.0	5.5	5.0	5.0

Table 17. Individual inspiratory time data, measured in seconds (sec) for the control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	0.99	0.92	0.96	0.87	0.79
2	1.20	1.23	1.21	1.20	1.26
3	1.34	1.14	0.92	0.83	0.87
4	2.03	2.13	2.14	1.22	0.99
5	1.03	0.96	0.94	0.91	0.88
6	1.36	1.11	1.16	1.11	1.19
7	2.86	1.53	1.71	1.59	1.47

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	0.74	0.64	0.60	0.60	0.58
2	1.00	0.93	0.91	0.93	0.88
3	0.97	0.89	0.75	0.67	0.62
4	1.26	1.20	1.09	1.02	0.94
5	0.56	0.58	0.63	0.59	0.55
6	0.76	0.68	0.72	0.63	0.72
7	0.91	0.72	0.66	0.72	0.71

Table 18. Individual expiratory time data, measured in seconds (sec) for the control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	1.32	1.17	1.28	1.20	1.04
2	1.42	1.54	1.54	1.57	1.60
3	1.84	1.47	1.18	1.04	1.09
4	1.81	1.92	2.08	1.34	1.12
5	1.11	0.96	0.94	1.00	0.94
6	1.80	1.56	1.50	1.74	1.73
7	2.22	1.38	1.44	1.15	1.12

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	1.20	0.75	0.74	0.72	0.75
2	0.93	0.89	0.88	0.93	0.92
3	0.94	0.87	0.72	0.66	0.54
4	1.08	1.02	0.94	0.89	0.76
5	0.53	0.56	0.59	0.59	0.55
6	0.86	0.88	1.07	0.69	0.96
7	0.69	0.68	0.65	0.65	0.63

Table 19. Individual total respiratory time, measured in seconds (sec data for the control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	2.31	2.09	2.24	2.07	1.83
2	2.62	2.77	2.75	2.77	2.85
3	3.18	2.61	2.10	1.87	1.96
4	3.84	4.05	4.22	2.56	2.11
5	2.13	1.92	1.88	1.91	1.82
6	3.16	2.67	2.66	2.85	2.92
7	5.08	2.91	3.15	2.74	2.58

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	1.94	1.39	1.34	1.31	1.33
2	1.93	1.83	1.79	1.86	1.80
3	1.91	1.76	1.47	1.34	1.17
4	2.35	2.22	2.03	1.90	1.70
5	1.09	1.14	1.22	1.17	1.10
6	1.62	1.55	1.78	1.31	1.67
7	1.60	1.41	1.31	1.37	1.34

Table 20. Individual duty cycle data for the control and CWR exercise condition

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	0.38	0.46	0.43	0.42	0.44
2	0.52	0.51	0.44	0.43	0.49
3	0.51	0.51	0.44	0.44	0.53
4	0.54	0.54	0.51	0.48	0.55
5	0.51	0.51	0.50	0.48	0.50
6	0.47	0.44	0.44	0.39	0.43
7	0.57	0.51	0.54	0.58	0.53

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	0.43	0.44	0.43	0.42	0.43
2	0.46	0.44	0.44	0.43	0.44
3	0.42	0.44	0.44	0.44	0.45
4	0.53	0.53	0.51	0.48	0.47
5	0.48	0.50	0.50	0.48	0.48
6	0.43	0.42	0.44	0.39	0.41
7	0.56	0.53	0.54	0.58	0.57

Table 21. Individual Poes time integrals, measured in cmH_2O per minute (cmH_2O/min), for the control and CWR exercise data

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	255	252	273	292	225
2	167	208	217	241	257
3	263	259	219	216	213
4				243	247
5	245	352	315	298	287
6		175		194	
7		270	316	352	380

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	331	294	313	311	295
2	79	161	89	100	128
3		299	372	303	304
4	130	189	271		198
5	243	279	190	233	121
6		162		167	
7	281	278	260	283	280

Table 22. Individual Pdi time integral data, measured in cmH_2O per minute (cmH_2O/min), for the control and CWR condition

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	236	231	257	254	196
2	333	381	210	371	438
3	141	178	177	190	166
4				329	263
5	181	197	250	237	256
6		218		240	
7		218	258	234	310

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	1093	891	933	955	840
2	1690	1516	1402	1499	1483
3		929	1246	909	954
4	677	833	903		1085
5	921	931	1008	942	975
6		670		541	
7	230	321	267	334	429

Table 23. Individual inspiratory elastic work of breathing data, measured in cmH_2O per minute (cmH_2O/min), for the control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	389	217	444	439	301
2	201	314	328	355	424
3	385	353	283	256	282
4		367	358	361	319
5	245	467	428	423	393
6					
7	338	306	336	360	340

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	174	330	357	367	420
2			444	475	502
3	297	338	352	331	331
4	135	149	230	300	181
5	469	528	495	529	548
6	134	188	196	280	266
7	215	330	272	309	353

Table 24. Individual inspiratory flow resistive work of breathing, measured in cmH_2O per minute (cmH_2O/min), for the control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	135	195	116	158	173
2	80	90	84	109	71
3	47	86	115	99	90
4			62	186	173
5	172	196	209	212	234
6					
7	223	159	207	281	339.09

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	180	296	385	334	423
2			353	382	446
3	141	167	241	237	263
4	120	156	227	223	191
5	209	272	273	291	308
6	30	69	79	125	88
7	220	281	283	285	342

Table 25. Individual total expiratory work of breathing (expiratory flow resistive work of breathing), measured in cmH_2O per minute (cmH_2O/min), for the control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	10	58	13	19	10
2	10	115	40	76	51
3	59	70	61	42	37
4		33	8	10	34
5	5	39	46	30	35
6					
7	50	95	27	77	109

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	43	88	172	13	25
2			12	1	1
3	11	167	87	115	188
4	107	145	93	84	283
5	83	181	86	120	164
6	0	11	7	30	42
7	127	154	198	133	220

Table 26. Individual total work of breathing, measured in cmH_2O per minute (cmH_2O/min), for the control and CWR exercise conditions

a. Control

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	369	436	376	419	360
2	282	376	383	364	374
3	223	247	286	247	309
4		172	242	349	383
5	294	574	574	544	555
6					
7	553	499	458	632	713

b. CWR

Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	372	663	859	703	738
2			556	564	671
3	332	425	590	584	717
4	346	428	512	547	638
5	635	862	717	805	886
6	58	183	207	323	328
7	517	706	694	681	858

Table 27. Individual peak Poes data, measured in cmH_2O, the during control and CWR exercise conditions

a. Control

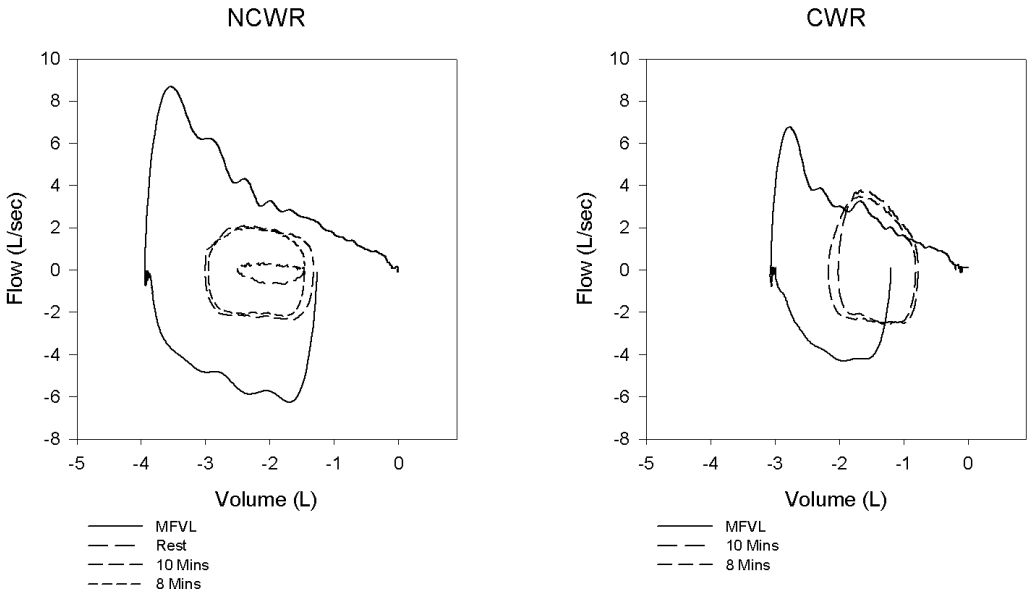
Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	-21.8	-26.3	-23.9	-23.8	-22.3
2	-15.9	-18.4	-19.1	-16.6	-22.2
3	-29.5	-22.5	-19.8	-21.1	-21.5
4	-18.1	-17.9	-18.6	-18.2	-16.1
5	-20.0	-22.9	-20.8	-21.0	-21.1
6	-23.8	-24.0	-25.0	-22.9	-23.1
7	-23.5	-28.2	-27.9	-26.5	-26.1

b. CWR

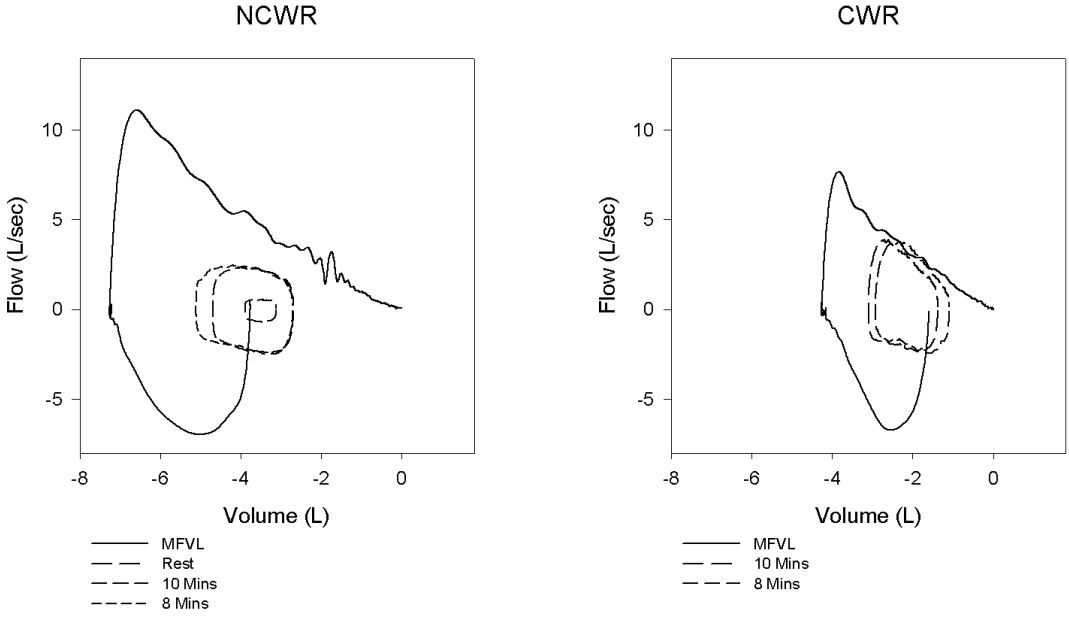
Subject	2 Mins	4 Mins	6 Mins	8 Mins	10 Mins
1	-21.7	-21.0	-22.6	-22.3	-20.6
2	-12.8	-15.0	-16.2	-16.1	-17.5
3	-18.1	-18.2	-18.5	-17.9	-15.6
4	-8.7	-9.1	-9.0	-9.9	-13.0
5	-15.7	-17.7	-17.7	-17.2	-14.9
6	-13.9	-13.3	-14.1	-12.8	-13.1
7	-19.0	-17.0	-18.9	-18.0	-19.5

Figure 17. Individual maximum flow volume loops with tidal breaths at rest (control condition only) and during exercise (8th and 10th minute). There are no flow volume loops for subject 2 as he could not perform the MFVL properly.

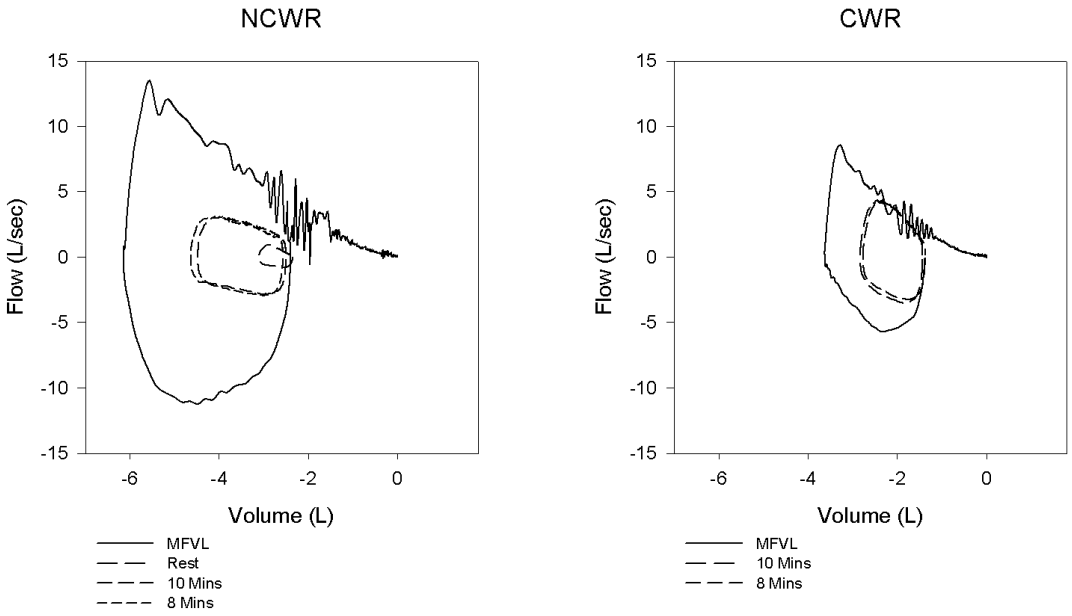
a. Subject 3



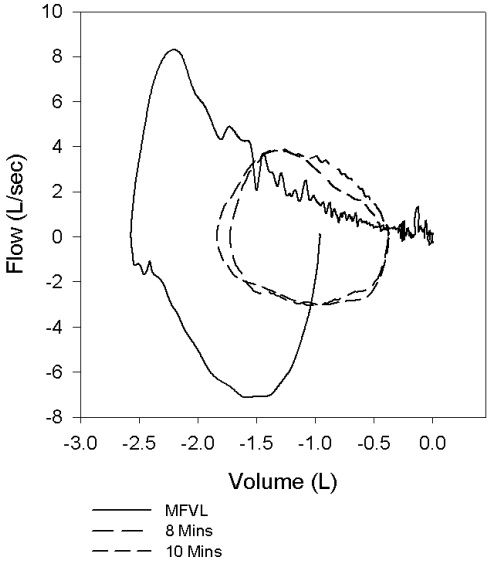
b. Subject 4



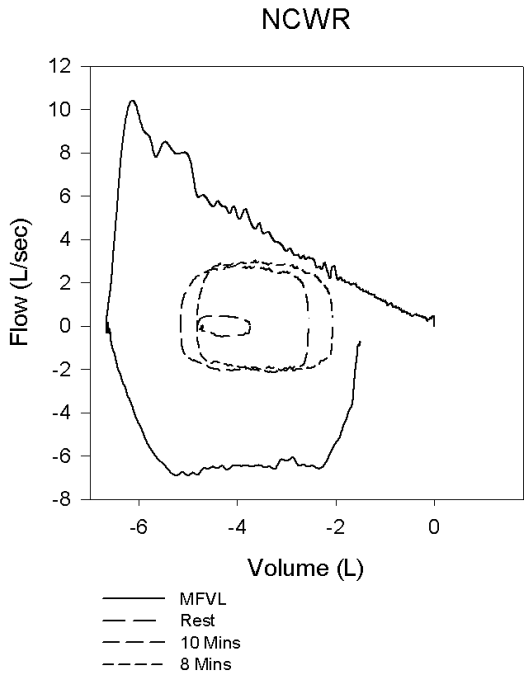
c. Subject 5



d. Subject 6 maximum flow volume loop for the chest wall restricted condition only



e. Subject 7


NCWR
Flow (L/sec)
12
10
8
6
4
2
0
-2
-4
-6
-8
-6
-4
-2
0
Volume (L)
MFVL
Rest
10 Mins
8 Mins

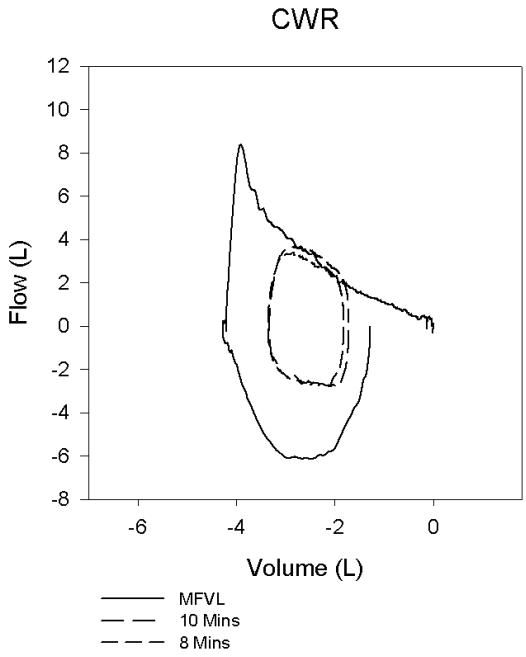
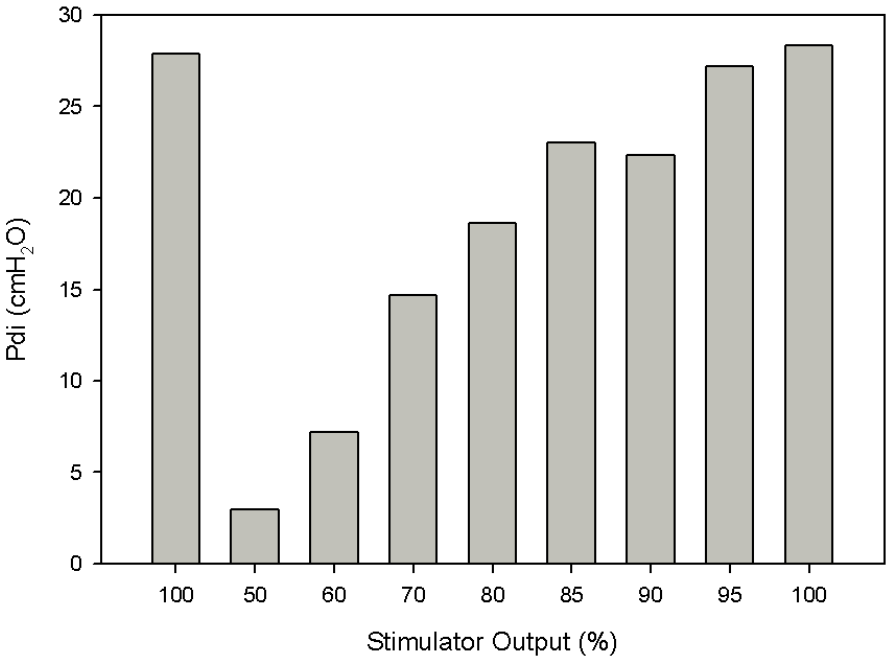
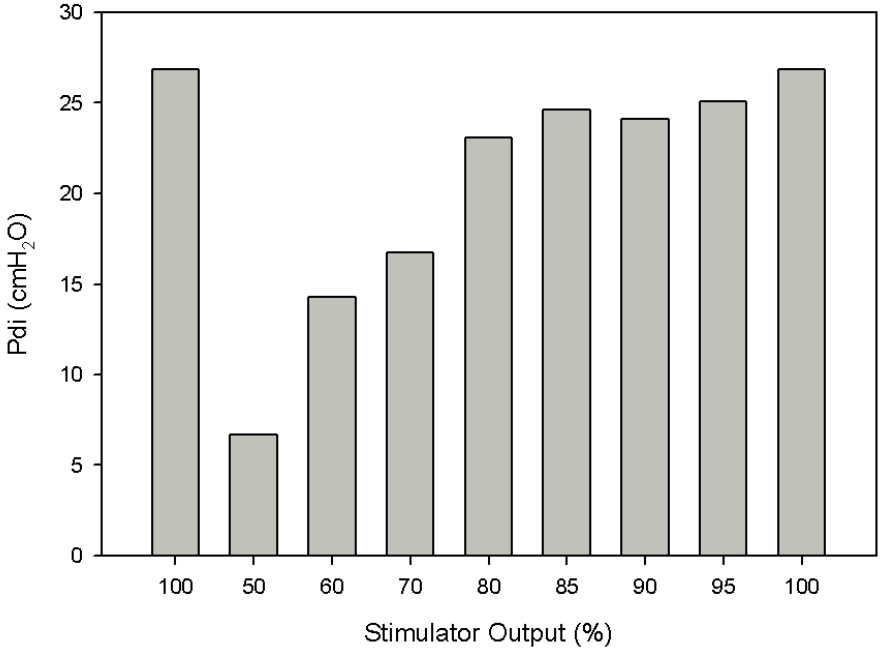

CWR
Flow (L)
12
10
8
6
4
2
0
-2
-4
-6
-8
-6
-4
-2
0
Volume (L)
MFVL
10 Mins
8 Mins

Figure 18. Ramp protocol for individual subjects

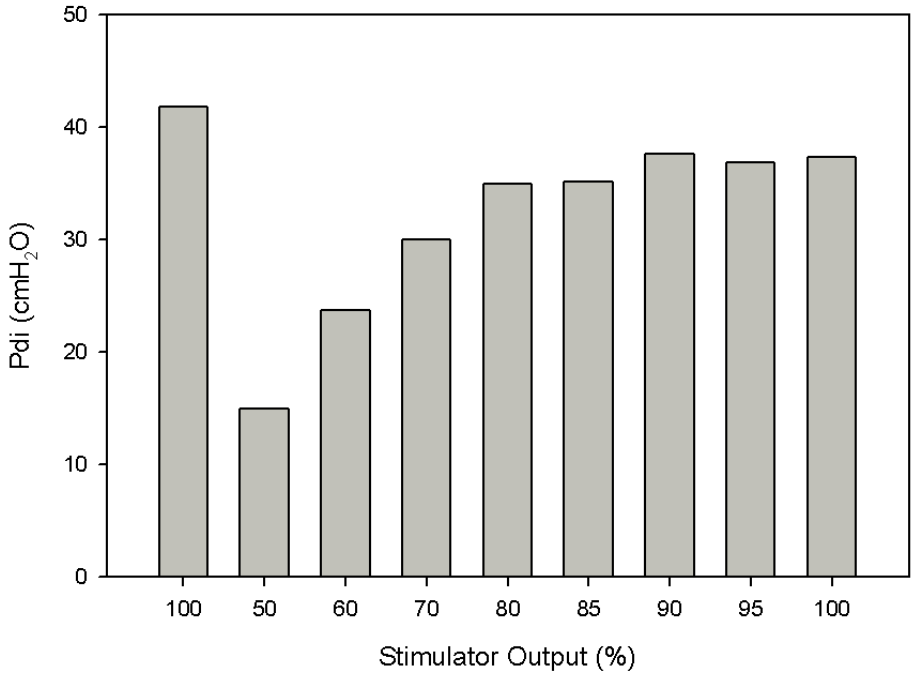
a. Subject 1



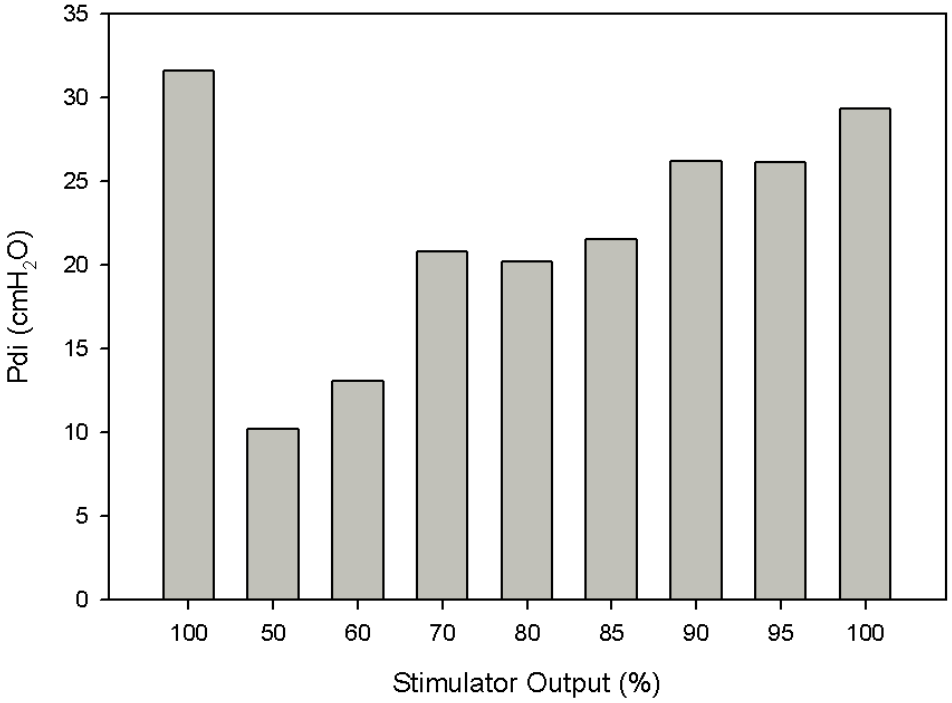
b. Subject 2



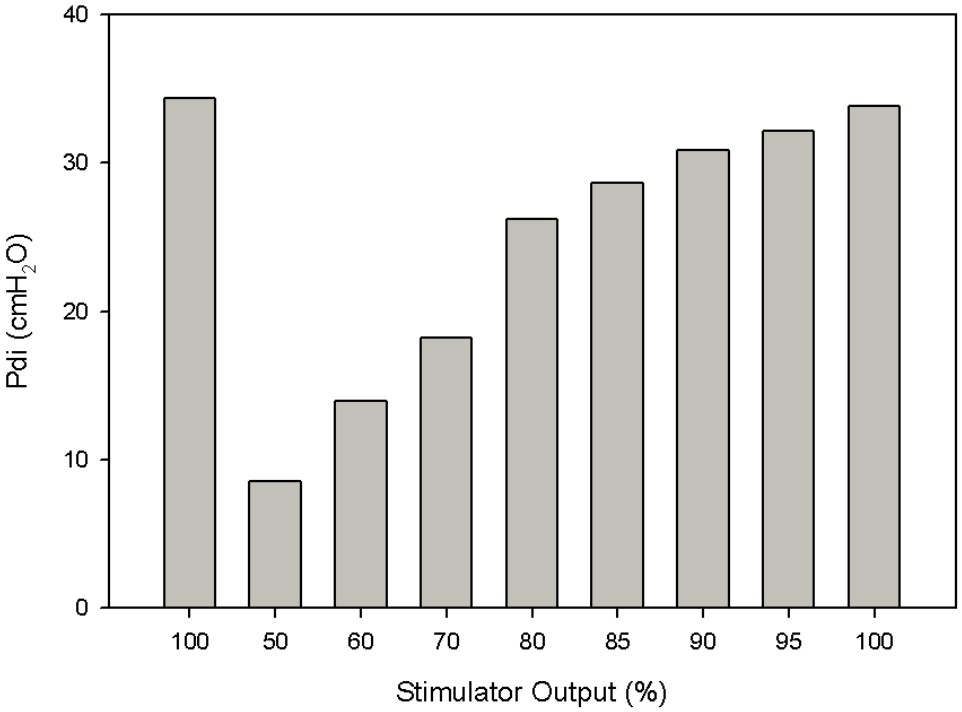
c. Subject 3



d. Subject 4

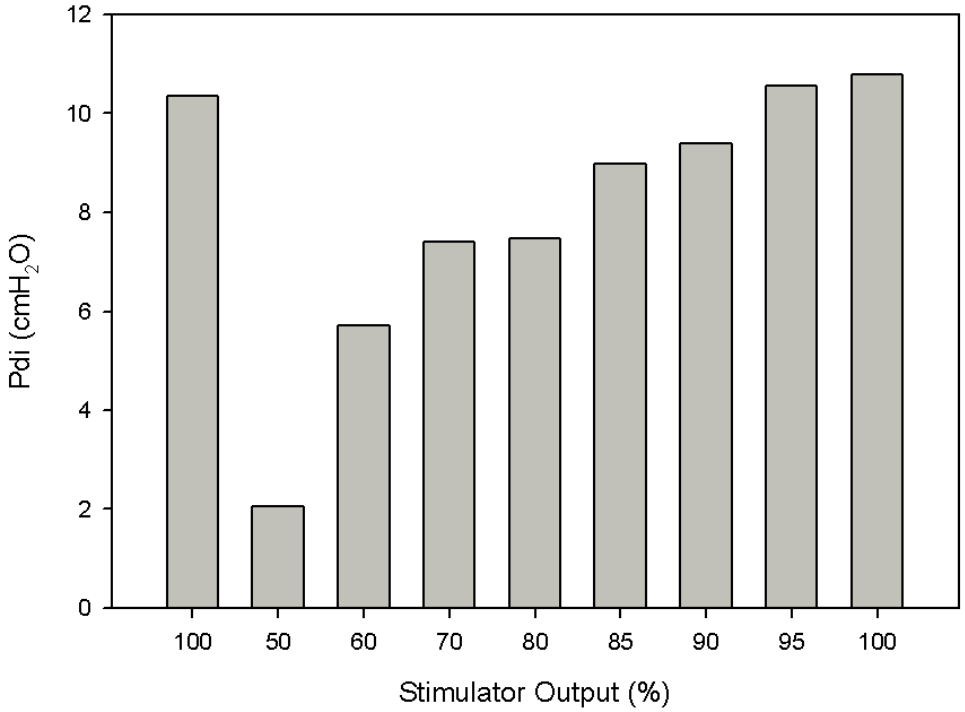


e. Subject 5



f.

g. Subject 6



h. Subject 7

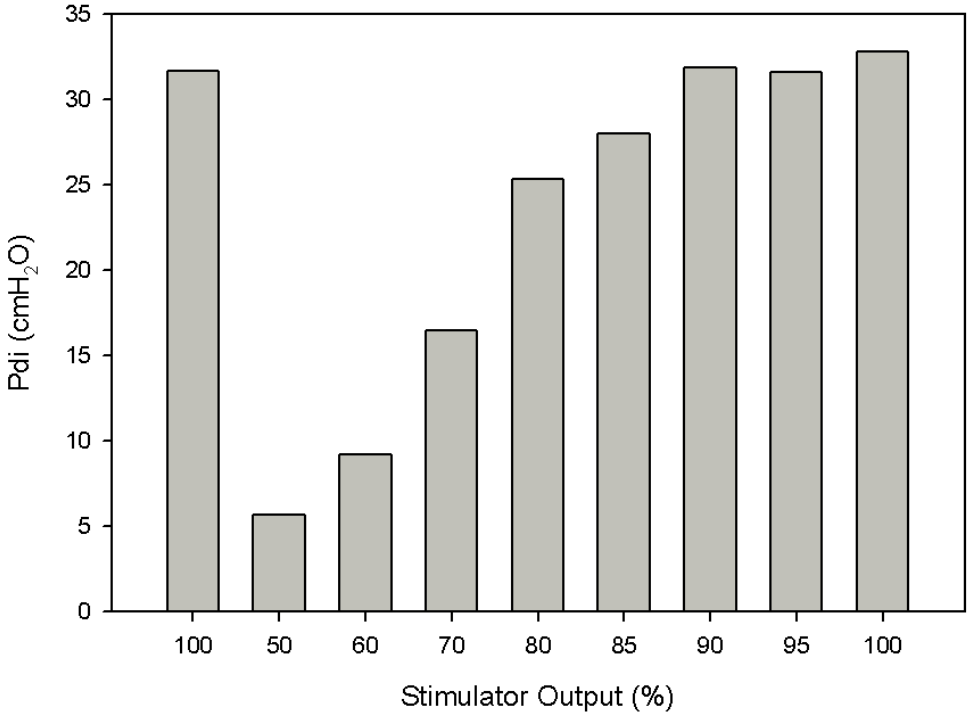

35
30
25
20
15
10
5
0
Pdi (cmH2O)
100
50
60
70
80
85
90
95
100
Stimulator Output (%)

Table 28. Review of literature on lung volumes, breathing mechanics, the work of breathing and diaphragm fatigue in restrictive disorders and chest wall restriction. Definition of symbols and abbreviations, N/R = not reported; √ = shown to occur; × = not shown to occur.

Study	FVC	Tachypnea	EELV	EFL	WOB	Diaphragm Fatigue
This Study	ê 40 % in CWR	√	é at end of CWR exercise in 3 subjects	√	é in CWR exercise	√
Miller et al. 2002	ê 38% in CWR	√	é at 45% VO_{2MAX}	×	é slightly in CWR exercise	N/R
O'Donnell et al. 2000	ê 35% in CWR	√	×	×	N/R	N/R
Harty et al. 1999	ê 44% in CWR	√	N/R	N/R	N/R	N/R
Hussain et al. 1985	ê	√	N/R	N/R	é	N/R
Johnson et al., 2000	ê 30% in CHF, from control	√	No change	√	N/A	N/R
Kufel et al., 2002	3.54 ± 0.55L in CHF (no control)	√	N/R	N/R	Pressure-time product of the diaphragm ($cmH_2O/s\sqrt{min}$) = 301.5 ± 64.2 (no control)	×
Mancini 1995	ê	√	N/R	N/R	é	×
O'Donnell et al., 1998	ê 70% in ILD	√	No change	√ in some subjects	N/R	N/R
Olson et al., 2006	ê	√	No change	√	N/R	N/R