PERCEPTION AND SUBJECTIVE RATINGS OF MULTIPLE BREATH RESISTIVE LOADS IN MALES AND FEMALES

By

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To my daughter, Amelia: Always follow your dreams. And breathe deeply.

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DSQ	Diagnostic symptom questionnaire
FEV	Forced expired volume
FVC	Forced vital capacity
LTA	Life threatening asthmatics
ME	Magnitude estimation
R	Resistive
SAM	Self-Assessment Manikin, an affective rating system to asses the three dimensions of pleasure, arousal and dominance
STAI	State Trait Anxiety Index, a 20-items questionnaire measuring anxiety as a trait or as a state
TV	Tidal volume

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Resistive (R) load magnitude estimation (ME) and subsequent subjective ratings were measured over multiple breaths in healthy subjects in two experiments. It was hypothesized that multiple breaths against a small resistive load will result in a decreased perceived load magnitude as the number of inspiratory efforts increase. It was further hypothesized that multiple breaths against large resistive loads will increase the perceived load magnitude as well as subjective ratings with increased breath number.

Subjects were screened by the experimenter, seated in a sound isolated room and respired through a non-rebreathing valve, the inspiratory port connected to the loading manifold. For study 1, the subject inspired to a peak airflow target for each breath. Each R load and no-loads were presented for 10 continuous breaths. The subject estimated the load at breath 1, 5, and 10 using a modified Borg scale. Each load was presented in a randomized block 3 times each in a single experimental session. For study 2, each R load and no-loads were presented for 20 continuous breaths. The subject estimated the load at breath 1, 10, and 20 using a modified Borg scale. Each load was presented in a randomized block 3 times each in a single experimental session.

For study 1, there was no significant sex group difference between the ME for breath 1 and 10 for small R loads, but a significant sex group difference for large R loads. The ME for males did not change between breath 1 and 10 for the small load magnitudes, but decreased with large loads. The ME for the 10 breath of the large R load was greater than the 1st breath for females. Males estimated the large R load on the 1st breath the same as females but the ME on the 10th breath was significantly less for males compared to females. For study 2, there was no significant sex group difference between the ME for breath 1 and 20 for small R loads, but a significant sex group difference for large R loads. The ME for males did not change between breath 1 and 20 for the small load magnitudes, but decreased with large loads. The ME for the 20th breath of the large R load was greater than the 1st breath for females. Males estimated the large R load on the 1st breath the same as females but the ME on the 20th breath was significantly less for males compared to females. Subjective responses of fear, fear of suffocation, happiness, chest pressure, faintness, dizziness, fear of losing control, trembling, tingling and unreality were significantly greater for females.

For study 1, these results demonstrate that magnitude estimation of large resistive loads with a sustained 10-breath trial elicits a significant increase in ME for females, but a significant decrease in males. The increase in ME may represent increased respiratory discomfort. For study 2, these results demonstrate that magnitude estimation of large resistive loads with a sustained 20-breath trial elicits a non-significant increase in ME in females, but a significant decrease in ME for males. The decrease in ME may represent increased adaptation to load. Loads larger than 15 $cmH_2O/L*s^{-1}$ elicited significant negative affect.

CHAPTER 1
INTRODUCTION

Inspiratory Loading

Inspiratory loading has been used to study the perceptual mechanisms underlying and mediating respiratory mechanical sensation and perception. There are several parameters to evaluate for breathing against loads: the mechanical effects on volume, flow or pressure; perceptual changes, magnitude estimation and anxiety response; changes in the nervous system; and blood chemical changes. To analyze perceptual changes in magnitude estimation and anxiety responses to inspiratory loads, it is necessary to analyze breathing pattern changes, perceptual reports, and subjective feelings associated with the inspiratory loads.

Most perceptual studies have examined the effect of a single-breath resistive inspiratory load. Single breath loading has been used to avoid the complication of changes in arterial blood gas and respiratory drive. One disadvantage of this is that single-breath mechanical loads are a poor simulation of disease states and may be of limited clinical significance. Physiologically induced inspiratory loads, such as those that occur during an asthma attack, require the patient to have sustained breathing periods against increased mechanical loading.

There are two primary cognitive components to the perception of increased respiratory load. The first is the somatosensory event. The second component is the cognitive evaluation of the load. Fundamentally, this means that the first event makes the subject aware that their load to breathing has changed and the second component involves the subject determining if the load is pleasant or unpleasant. Subjects seldom report unpleasant evaluations of single breath loads. However, it is likely that as a person increases the duration of breathing time against a load, subsequent unpleasant sensations arise. The cognitive response to breathing against sustained inspiratory loads has not been investigated.

Cognitive analysis of respiratory challenges can vary among subjects. Davenport and Kifle (2001) reported that estimation of the magnitude of inspiratory resistive loads was reduced in children with life threatening asthma. It is known that patients experiencing increased mechanical loads to breathing have an increased incidence of affective disorders such as anxiety (Put 1999). Some subjects, such as females and high trait anxiety subjects, magnify their perception of loads, which in turn increases their negative affect.

The purpose of this study was to determine the ventilatory adaptation of breathing pattern against sustained loads and the changes in perception of breathing as the subject respired against an elevated load over a prolonged period of time. It is also likely that there are sex differences in the responses in ventilatory pattern, airflow and timing to breathing against elevated inspiratory loads. Thus, a second component of this study is to determine the relationship between perception of loads applied over multiple breaths and sex. We hypothesized that prolonged inspiratory loading alters ventilation, perception, and subjective ratings of the loads in both males and female subjects. We further hypothesize that males and females differ in their subjective and objective discrimination of the load, but will not differ in their ventilatory response.

Breathing Mechanics

Ventilation of the lung is a mechanical process. The respiratory muscles act as a pump to generate the driving force for air to flow and increase the lung volume. Application of extrinsic mechanical loads of sufficient magnitude will alter this mechanical process and lead to a conscious awareness of the loads (Wiley 1966; Noble 1972; Campbell 1961; Buki 1983; Bennet 1962).

The mechanical output of breathing is commonly measured in terms of tidal volume and frequency. Thereby all the complex movements of the respiratory system are integrated into a minute ventilation (Mead 1973). There are two components to the volume dimension: the first is the volume displacement of the rib cage, and the second is of the abdominal surface. Muscles intrinsically compensate for loads which limit respiratory muscle shortening. The diaphragm is predominantly positioned to respond intrinsically to a common and natural form of loading. However, certain loads, such as rib compression and steady positive pressure breathing, tend to increase the degree of diaphragmatic shortening.

Body wall expansion is mainly in the antero-posterior (A-P) direction in humans. At a given lung volume, with the spine held in a fixed attitude, it is possible to change the shape of the body wall, mainly in the A-P dimension (Mead, 1973). If airway pressure is held near atmospheric to avoid large changes in pleural pressure, these changes in shape involve reciprocal movements of the rib cage and abdomen (Mead, 1973). As the rib cage is expanded, the abdomen is pulled in. If substantial changes in pleural pressure are allowed, the A-P diameter of the rib cage can be changed without reciprocal changes in the abdomen. The A-P diameter will decrease as pleural pressure decreases.

The diaphragm's action on the rib cage is twofold, both direct and indirect. The diaphragm acts directly on the rib cage by elevating the costal arch and indirectly by lowering pleural pressure (Kuno and Mead, 1973). Changes in rib cage characteristics are due to the action of the passively tensed diaphragm on the rib cage. As lung volume is decreased, the relaxed diaphragm is lengthened and develops passive tension. When external pressure (mechanical or physiological) is applied from the outside to the respiratory system, the pressure is dispersed across the lungs and the chest wall. The applied pressure drives the two in series. When ventilation is increased, the action of the abdominal muscles is to reduce the swing in abdominal pressure to take the load off the diaphragm.

Breathing Response to Loads

Loads: Loads can be inspiratory or expiratory. Mechanic loads are divided into three main types: resistive loads, in which the load is proportional to the flow; elastic loads, in which the load is proportional to displacement; and threshold loads, in which the load is independent of flow or displacement (pressure breathing) (Otis 1973, Howell 1973). Magnitude estimation and load detection studies have been done using inspiratory resistive loads (Wiley and Zechman, 1966; Muza 1984; Davenport 2000; Webster and Colrain, 2000). The detection of added resistance to expiration or inspiration follows the same relationship, as reported by Wiley and Zechman (1966). Similar muscle receptors and neural processing systems are utilized in the estimation of added loads involving either inspiratory or expiratory muscle groups (Muza 1984). For the experiments in this dissertation, inspiratory resistive loads were used.

Freedman and Campbell (1970) investigated the ability to tolerate maximum levels of the three types of loads: elastic, resistive, and threshold, the latter being equivalent to a fixed pressure which had to be developed before any gas flow could occur. Elastic and threshold loading resulted in inter-individual variation, with a non-significant increase in all submaximal loads. The pattern of breathing was consistently altered by elastic and resistive loads. Resistive loading has been shown to slow the frequency of breathing compared to elastic loading (McIlroy et al., 1956; Pope, Holloway and Campbell, 1968). This is due to a prolongation of the phase of respiration that is loaded and the prolongation is proportional to the size of the load (Zechman, Hall and Hull, 1957).

Experimentally applied external loads to breathing are generally symmetrical in the sense that they load the system in its common path, the airway (Mead et al., 1973). They are tightly controlled and uniformly given across subject populations. Natural loads are more commonly asymmetrical, influencing one part of the system more than another. Most pulmonary diseases have as increased respiratory load as one component to the disease process. The central nervous system is adapted to compensate for changes in natural loads. For example, when nasal resistance is excessive, we switch to mouth breathing,. Natural loading also occurs with sleep-induced increased airway resistance, and increased abdominal loading in the form of tight clothing or pregnancy result in an increased drive to breathe.

Ventilatory response to loads: Breathing pattern responses to added resistive and elastic loads are affected by both brainstem neural reflexes and supramedullary behavioral reactions following conscious perception of altered breathing mechanics (Daubenspeck & Rhodes, 1995). Adding resistive loads (ΔR's) to respiration changes airflow, volume, and pressure and the magnitude of the external load determines the degree of change (Kellerman et al. 2000). Most people, when presented with a moderate inspiratory resistive load, adjust breathing pattern to the type and magnitude of the load and maintain constant alveolar ventilation (Laviettes et al., 2000). The compensation of ventilation with maximally tolerable loads is to reduce subjective discomfort (Freedman and Campbell 1970) and ventilatory pattern is optimized to reduce respiratory sensory input to minimize uncomfortable breathing sensations (Cherniack et al., 1996; Oku et al. 1993). Individual differences in load responses are primarily due to behavioral (i.e. voluntary) responses in an effort to minimize abnormal respiratory sensations (Younes et al., 1995). Inspiratory airflow and volume change little when respiring against small loads near the detection threshold, but transdiaphragmatic pressure increases significantly (Zechman et al., 1985). It is common for some subjects, including asthmatic patients, to decrease inspiratory flow during a resistive loaded breath (Kifle et al., 1997). Resistive loads are airflow-dependent loads and a decrease in the inspiratory airflow reduces the pressure and airflow changes associated with the increased load. Tidal volume (VT) is usually preserved when conscious humans are made to breathe against an inspiratory resistance. This compensation is accomplished through increasing pressure peak amplitude, increasing duration of the pressure rising phase, and the rising phase becoming more concave to the time axis (Hof et al., 1986).

The ventilatory response to added mechanical loads can be regarded as the sum of two components: one representing the effect of the passive respiratory system and one representing the effect of neural load-compensating mechanisms (Axen et al., 1982). The load compensating component represents the action of neural mechanisms that modify the pressure developed by loaded respiratory muscles (Zhao et al., 2002). Receptors in lung and lower airways can contribute to these neural adjustments. In both double lung transplant (DLT) patients and healthy subjects, increases in the magnitude of resistive loads results in an increased mouth pressure (Pm), inspiratory time (TI) and pressure and a decreased inspiratory volume (VI), airflow, expiratory time (TE), frequency (f) and expiratory volume (VE) (Zhao et al. 2002). This indicates that in conscious humans, load compensation can occur in the absence of vagal afferent input, as long as the remaining afferent pathways are intact.

The cerebral cortex plays a significant role in the processing of sensory information related to mechanical effort and many aspects of respiration. Consequently, the cerebral cortex is one neural component mediating the magnitude estimation of a load applied to breathing. The estimation of the magnitude of a load, along with initial detection of that load, is mediated by cortical processes, presumably within primary somatosensory and association areas (Webster 2000). The activation of cortical neurons by mechanical loads has been studied using evoked potential techniques similar to techniques used in other somatosensory systems (Davenport 2000; Davenport 1996; Davenport 1986; Logie 1998; Revelette 1990; Strobel 1993). Previous human studies have shown that inspiratory and expiratory occlusion and mechanical loading will elicit

EEG activity in the form of a respiratory related evoked potential (RREP). (Davenport et al., 2000; Gora et al., 1999, 2002; Webster et al., 2002; Webster and Colrain, 1998, 2000a, b, 2002). Human subjects are consciously aware of breathing against mechanical loads (Williams et al., 1988). Respiratory psychophysiological research demonstrates that the regulation of breathing is significantly impacted by behaviorally controlled processes in higher brain centers (Wientjes & Grossman 1998; Cherniack 1996; Oku et al., 1993; Plassman, Lansing & Foti 1987; Shea & Guz 1992; Wientjes, Grossman & Gaillard 1998).

There are several aspects to consider when applying external loads to the respiratory system. Precise measures of breath-to-breath variations in ventilation are allowed when subjects breathe on a mouthpiece with a nose-clip in place, but breathing through equipment alters respiratory somatosensation and output. The two main variables that influence respiratory recordings are apparatus and instructions (Harver and Lorig, 2000). Golla and Antonovich (1929) reported that "any attempt to breathe through an open mouthpiece or mask, which is to say a piece of apparatus with centers the subject's attention on his breathing, invariably gives rise to an abnormal type of respiration." For this reason, it is necessary to include no-load presentations (R=0 cm H20/l/s) to control for apparatus or instructional effects. The second interference to consider is the effect that occurs when an experimenter instructs a subject on a breathing task and with the subject's response to increase airflow resistance (Wigal et al., 1997). Improvement in respiratory function followed suggestions of bronchodilation, and when suggestions of bronchoconstriction were presented, deterioration in respiratory function was seen (Falkner 1941; Kotses 1998). This has been demonstrated in both healthy subjects as well as patients with lung disease (Kostses et al., 1987a; Ketses et al 1989). The effects of suggestion are derived from the anticipation of the administration of the substance, as a component of the threat of aversive stimulation (Kose et al., 1989). Instruction to subjects to breathe normally will often result in arrhythmic and irregular breathing patterns (Harver and Lorig, 2000), which is why it is necessary for the subject to breathe through the mouthpiece for several minutes to adapt to the experimental apparatus.

Multiple Breath Resistive Loads

Axen et al. (1983) examined load-compensating behavior using the ventilatory response to 10-breath resistive loads by men and women with 160 subjects (80 males and 80 females) and found the sex related responses similar but not identical. They reported in conscious humans, sustained breathing with mechanical loading activates neural load-compensating mechanisms, the range of these neural adjustments varies with both load size and type, and the stimulus to initiate this behavior was mainly non-chemical. During the first, fifth and tenth consecutively loaded breath, individual responses ranged from a rapid-shallow to slow-deep breathing pattern; strong tidal volume defenders employed longer inspirations than weak tidal volume defenders; and individual frequency responses were mediated by changes in inspiratory or expiratory timing. The group response was qualitatively similar on the 1st, 5th, and 10th breath. Tidal volume responses do not differ significantly. Axen et al. (1984) demonstrated that men actively prolonged inspiration more than women during resistive loading and women actively shortened inspiration more than men during elastic loading. In response to extended loads, mean inspiratory airflow response of women exceeded those of men by an amount attributable to women's higher intrinsic respiratory resistance. However, no studies have been done to compare the ventilatory response of extended loads or the magnitude estimation of these loads.

Laviette et. al (2000) examined the perception on a modified Borg score of dyspnea as well as the ventilatory response to small sustained resistive loads of 1.34 cmH2O/l*sec-1 and 3.54 cmH2O/l*sec-1. This study demonstrated that there was a subset of subjects who, when compared with the remainder of the study group, consistently reported increased dyspnea with repeated inspiratory loads. The authors reported that any differences in Borg score responses between groups could not be explained by differences in physiological responses to the load, since subjects maintained constant ventilation despite increasing scores of dyspnea. However, although Borg scales of dyspnea were measured, magnitude estimation of loads were not examined, and their subject pool was predominantly female so no sex effects were analyzed.

Perception of Breathing

Respiratory perception is a result of the physical awareness (what is sensed) and affective judgment (how it feels) and appears to be a 2-stage process. Stage 1 is the discriminative dimension and includes the awareness of the spatial, temporal and intensity components of the respiratory disruption. In this stage, respiratory somatosensation generated by the discriminative awareness of respiratory stimuli is determined by the interaction between multiple respiratory afferent groups and brainstem respiratory motor drive. The second stage, the affective dimension, is a potentially important but little explored aspect of respiratory sensory processing. Subsequent to initial somatosensation, respiratory stimuli can evoke distress and motivate cognitive behavior. It is possible that distressing respiratory sensations may condition human subjects to have a heightened awareness of their breathing and may even induce respiratory related anxiety. Humans can easily discriminate the presence and type of respiratory mechanical loads, estimate the size of the loads and scale these respiratory mechanical stimuli.

The perception of respiratory sensations has been examined by asking subjects to estimate the sensory magnitude of a suprathreshold load, using a numerical scale (Kelsen 1982, Kifle 1997; Killian 1981; Lansing 1996; Moy 2000), visual analogue scale (Lansing 1996; Bijl-Hofland 2000), and cross-modality matching (Burki 1984; Burki 1983). These studies have been done using single-breath resistive loads. The subjects then estimate what they feel as a numerical correlate of the load magnitude on a scale of 0-10. For the present study, we chose to utilize a numerical scale for magnitude estimation to represent respiratory perception and numerical and visual scales for subjective responses.

Some subject groups, such as children with a history of life-threatening asthma, have a unique decreased perceptual reactivity to resistive loads, which cannot be explained by differences in respiratory effort, airway mechanics, or task performance ability (Kifle, Seng & Davenport, 1997; Kikuchi et al., 1994). These patients have a unique perceptual processing deficit to respiratory loads (Davenport, et al 2000). Webster and Colrain (2000) reported that this deficit may be due to a problem in the transduction of afferent neural signals originating in muscle stretch receptors and projecting to somatomotor cortical regions. It is possible that there are additional subject groups affected by blunted respiratory perception.

Knafelc and Davenport (1997) investigated the relationship of the respiratory related evoked potential to the perception of inspiratory resistive load, using increasing magnitudes (2, 9, and 21 cmH2O/l*sec-1). The reported that the amplitude of P1 significantly increased (R2=0.99) with increases in resistive load magnitude. There was a significant log-log relationship (R^2=0.996) between magnitude estimation and RREP P1 amplitude. Knafelc and Davenport (1999) also reported similar results using two direct measures of inspiratory mechanical effort, transdiaphragmatic pressure and esophageal pressure.

Human subjects can easily detect and scale mechanical loads (Kelsen et al., 1982, Kifle et al., 1997; Killian et al., 1981; Lansing et al., 1996; Bijl-Hofland et al., 2000; Taguchi et al., 1991; Burki et al., 1984; Burki et al., 1983; Burki et al., 1978; Bennett et al., 1962). The respiratory load detection threshold is a psychophysical measure of respiratory perception (Zechman et al., 1986). Zechman et al., (1986) reported that the perceived magnitude of a load is linearly related to the added load when a log-log transformation is used. The slope of this relationship is an index of the perceptual sensitivity for the type of load presented. A low slope value is indicative of poor perception (Julius et al., 2002). Alternatively, a high slope value is indicative of increased perception. Numerous studies conclude that respiratory perception with added inspiratory resistive loads follows Stevens' psychophysical power law (Burki et al., 1980; Gottfried S et al., 1981; Killian et al., 1982; Killian et al., 1981; Wiley et al., 1978). Consequently, perceived magnitude (ψ) of a stimulus is related to the physical magnitude of the stimulus (φ) by a constant (k) and an exponent (n): $\psi = k\,\varphi^{n}$., where k is a measure of the threshold and the exponent, n, is a measure of perceptual sensitivity. The exponent is determined by calculating the slope of the log-log relationship between load magnitude (φ) and magnitude estimation (ψ). In inspiratory resistive loading studies, the stimulus is the magnitude of the added inspiratory resistance. It has been suggested that the sensory perception of the pressure generated by inspiratory muscles against resistive loads might be important in assessing the magnitude of these loads (Killian et al., 1982; Altose et al., 1981).

Individual differences in the perception of added loads do not correlate with differences in age or measures of lung function (Freedman and Campbell, 1970; Julius 2002). Several studies have determined that intolerance of the loads could not be explained as being due to any of the following variables reaching a critical or limiting value: ventilation, tidal volume, frequency, peak mouth pressure, peak inspiratory flow rate, added inspiratory work or power and end-tidal PCO2 (Freedman and Campbell, 1970; Julius et al., 2002). Since simple ventilatory and mechanical parameters to explain the subjects' ability or otherwise to tolerate (or not) certain levels of loading were insufficient, subjective psychological factors may be important in determining load perception.

Load detection, used to measure the ability of subjects to detect loads, has a resistive threshold which is the resistive load magnitude at which 50% of the presentations will be detected. The load-detection threshold has been shown to be a constant fraction of the background load intrinsic to the respiratory apparatus and the subject's intrinsic airway resistance (Wiley et al., 1966). The second perceptual process includes differentiation of the load type and the accompanying estimation of the load magnitude (ME). Subjects are usually presented a single breath load and required to provide an estimate of the sensory magnitude of a suprathreshold load using a numerical scale or cross-modality matching, such as handgrip tension sensation to match the magnitude of respiratory sensation. In the present study, we will build upon previous studies in our lab testing the subject response to sustained loads measuring magnitude estimation and subjective symptoms.

Psychophysical studies of respiratory load perception have been conducted in asthmatic and non-asthmatic subjects using external resistances (Julius et al., 2002). These studies have shown considerable variation among subjects in the detection and ME of both intrinsic and extrinsic resistive loads and the perceived effort of breathing. Hudgel et al. (1982) reported that anxious subjects selected from normal hospital workers, required higher inspiratory resistances for load recognition than non-anxious subjects. It has also been demonstrated that subjects with generalized anxiety or panic disorder were unable to grade the magnitude of a series of inspiratory resistances (Tiller 1987). This suggests that psychological state significantly contributes to or alters the perception and scaling of loads.

Sex Differences

Female lungs tend to be smaller and weigh less at necropsy than male lungs (Thurlbeck et al., 1982). Typically, females have smaller lung volumes, lower maximal expiratory flow rates and smaller diffusion surfaces than males, which result in lower maximal pulmonary ventilations

(Mead et al., 1980; McClaran et al. 1998). Women tend to be of smaller stature and trunk size than men, but these differences remain when body size is taken into account (Mead et al., 1980; Thurlbeck et al., 1982; McClaren et al. 1998). Tatsumi et al. (1991) did systematic comparisons of resting ventilation and hypoxic ventilatory response in awake male and female cats, determining no physiological differences in baseline ventilation once body size was accounted for. Discrepancies in reports demonstrating sex differences in mean ventilation are seen (Kilbride et al. 2003), although some reports of sex differences in resting mean ventilation have been reported, with higher mean ventilation in males compared to females (White et. al. 1983; Aitken et al. 1986; Goldstein et al., 1987; Regensteiner et al. 1988). The control of breathing is influenced by sex-specific events such as changes in the estrus cycle, pregnancy, and menopause (Regensteiner et al., 1989). Males have reported higher urge to breathe during exercise, but this difference can be accounted for due to the absolute workload for males being higher than for females due to body size differences (Kilbride et. al., 2003). However, the sex-related perceptual differences in magnitude estimation of sustained resistive loads have never been studied.

Men and women have differences in their physiological makeup that could result in a minor difference in responses to inspiratory resistive loads. Men actively prolong inspiration more than women during resistive loading, and women actively shorten inspiration more than men during elastic loading (Axen 1984), although these differences do not reach statistical significance. The load-compensating behavior exhibited by men and women is similar and tidal volume responses to loading do not differ (Axen 1984). In addition to physiological differences, Axen et al. (1984) first suggested that men and women could perceive the same load differently, due to the fact that load detection capability depends on intrinsic impedance (Wiley 1966). Intrinsic impedance is due to mechanical properties of the respiratory apparatus.

Sociocultural factors also play a role in the sex differences in the perception, reporting, and diagnostic interpretation of respiratory symptoms such as shortness of breath, cough, sputum production, and sleep disordered breathing (including snoring) with all except shortness of breath being less commonly reported by women than by men (Schwab et al., 1999, Knauffman et al., 1996). Shortness of breath is a symptom commonly reported in chronic obstructive pulmonary disease (COPD) (Dodge 1986), and is consistently higher for females than males (Dales et al., 1989; Krzyzanowski et al., 1992; Krzyzanowski et al., 1986; Guslvik et al., 1979) despite higher mortality rates due to COPD in males (Thom 1989; Vollmer et al., 1992). A study of over 20,000 participants spread over 7 cities in France demonstrated reporting rates for shortness of breath decreased with increasing levels of forced expired volume (FEV1) in a similar fashion in both men and women, at all levels of FEV1 reporting rates were higher in women than in men (Knauffman 1996; Krzyzanowski 1988). These sex differences not only remained but increased after standardizing for potential confounders such as smoking, occupational exposure, educational level, obesity, and FEV1 level (Knauffman 1996; Becklake 1999).

The perception of altered respiratory function by women may be more sensitive but less specific than by men (Becklake and Knauffman, 1999). Dyspnea is perceived as more important in women's quality of life scales than in men's (Jones 1992). Becklake and Knauffman (1999) also reported psychological factors such as depression have been linked to the reporting of respiratory symptoms, though sex differences in rates of reporting by psychological status have not been examined. The current study further expands this research by examining psychological measures with an altered respiratory load by adding inspiratory resistive loads.

Takano et. al. (1997) and Becklake et al. (1999) reported that differences may exist between males and females in the perception of respiratory discomfort. Women with respiratory disorders such as COPD self-report more psychological distress than men (Laurin et al., 2007). Laurin et al. (2007) reported that psychiatric disorders, which are three times more common in COPD patients than in healthy subjects. Among COPD patients, psychiatric disorders are nearly two times higher in women than in men (Laurin et al., 2007). Female patients are more exposed to psychological impairment that correlates well with the dyspneic component of chronic obstructive pulmonary disease (Di Marco et al. 2006). When patients are affected by pulmonary disease, women report less confidence in their ability to control their respiratory symptoms and have less total and activity-related quality of life compared to men (Laurin et al., 2007.)

In general, psychiatric disorders are more common in women than in men (Laurin et al., 2007; Kessler et al 1994). In addition to psychiatric disorders, adults admitted into the hospital with asthma are significantly more likely to be female (Woods et al., 2003; Senthilselvan et al., 1995; Hyndman et al., 1956; Wilkins et al., 1993; Rao et al., 2003). Measures of asthma morbidity have been shown to be disproportionately higher in females (Woods et al., 2003) and there is a higher trend for female readmission (Chen et al., 2003).

Females tend to have a greater sensitivity to their perception of physical stimuli. Edwards et al. (2003) reported significantly greater pain sensitivity in females for both experimental and clinical pain. Females in the general population report a greater frequency, intensity and duration of pain-related symptoms than adult males do (Edwards et al., 2003). Thus, it is hypothesized that females and males will differ in subjective symptom expression with sustained breathing against inspiratory resistive loads.

Anxiety and Respiration

Anxiety can be broadly defined as an emotion that entails the appraisal of threat that is uncertain or uncomfortable (Rachman, 1998; Speiberger, 1972) and is associated with subjective feelings of apprehension about impending or anticipated harm. Five items in the Autonomic

Perception Questionnaire (Mandler et al., 1958) relate to changes in breathing that occur with anxiety, and respiratory signals are prominent indicators (along with cardiovascular and electrodermal signals) of dececption (Horowitz et al. 1997; Patrick & Iacono 1991). Anxiety is associated with respiratory changes such as hyperventilation and dyspnea. Increased ventilation is a physiological state change and is a component of a defense mechanism, the fight-or-flight response, which is an adaptive response to danger that is largely sympathetically mediated and prepares an individual for immediate action (Van Diest et al., 2001; Gardner 1994). This increase in ventilation can lead to a drop in PCO2 level (hypocapnia). Ley & Yelich, 1998, showed that hypocapnia can be induced experimentally in healthy individuals by making them anxious. Respiratory pattern reflect emotions to the same extent as facial muscles (Feleky 1916). Variations in the ratio of inspiratory and expiratory times for disgust, pleasure, anger, pain, wonder, and fear provide compelling evidence for the specificity of emotional expression in the respiratory system (Harver and Lorig, 2000).

As the perception of ambiguous and unpleasant sensation serves to exacerbate symptoms, patient's emotional reaction to a sense of breathlessness exacerbates their perception of breathlessness (Bailey et al, 1994). Anxious patients report the subjective experience of an "inability to get enough air into the lungs" and "a sense of oppression or suffocation" (Christie 1935). Several studies suggest that stress/anxiety is related to the over-perception of respiratory symptoms, but the mechanism underlying this association remains unclear (Put et al., 1999; Put et al., 2000). Subjects that associate high ratings of dyspnea with relatively small inspiratory loads are considered "symptom amplifiers" (Lavietes et al., 2000). Although the ventilatory response to loads is governed primarily by respiratory system mechanics, respiratory reflexes, behavioral and cognitive factors may play a role in this response as well (Hudgel et al., 1982;

Tiller et al., 1987). Cognitive factors can modify a subject's load response by symptom amplification, or they may exhibit an exaggerated subjective response to a load. Subjects who exaggerate subjective responses tend to be more anxious, self-conscious and have low self esteem, and may be more likely to report other symptoms as well (Schwartz et al. 1978; Taylor et al., 1953; Lipman et al., 1969). Also, subjects with anxiety or depression may demonstrate enhanced physiological or ventilatory responses to a load when compared to control groups. Laviete et al. (2000) showed that subjects with higher ratings of perception also had increased Ve in the presence of small and large loads, and were more unlikely to maintain constant ventilation. This suggests that subjects who are "symptom amplifiers" or "overperceivers" may have increased ventilation with inspiratory loads.

High anxious subjects had a higher minute ventilation to a CO_2 challenge in conditions of minimal information and control when CO_2 is given first, suggesting an important order effect for high-anxiety subjects. The subjects continue this breathing pattern during room air trials, and the pattern is not observed when the placebo is given first or when the trial was predictable and controlled (Van De Bergh et al, 1995). This suggests a respiratory learning effect, which can be offset by providing verbal information about the procedure.

There are many cortical and sub cortical projections to the brainstem, where the respiratory center is located, that may influence breathing. As a result, even a brief thought of a stressful event may significantly influence breathing pattern. Masaoka and Homma, (2000) demonstrated an increase in respiratory frequency was observed during anticipation of anxiety. They used the dipole tracing method to investigate brain activity synchronized with physiological responses. Neural activity (electric current sources during anticipation of anxiety) was found in the right temporal pole and left amygdala and synchronized with the onset of inspiration. The amygdala plays a role in human emotions such as fear and anxiety (Davis et al., 1992). These areas associated with anxiety directly produce respiratory change. Respiratory discomfort has been demonstrated in brain imaging studies to involve the activation of the limbic and cerebellar regions of the brain.

Breathing is controlled unconsciously but can be consciously modulated. Similarly, human fear and anxiety responses are clearly mediated by both conscious and unconscious processes. Respiratory instability may reflect a thinking style that emphasizes intensely stressful cognitions. Individual levels of anxiety affect respiratory frequency, especially expiratory time in normal subjects (Masaoka and Homma, 1997). Masaoka and Homma (2001) determined that "trait anxiety" not only determines the strength of the emotion of anxiety in individuals, but also influences behavioral breathing independently from metabolic demands. Anxiety itself may enhance involuntary muscle contraction and possibly cause a respiratory change.

Disruption to breathing can be highly distressful. Harver and Lorig (2000) report that "Individuals sensitive to their breathing continue to be concerned about their physiological state, and in a classic feed-forward loop, exhibit further hyperventilation and an array of symptoms including shortness of breath, dizziness, chest tightness and chest pain. The event itself becomes anxiety-provoking, and individuals become fearful of repeating the incident, effectively making the next even seem more stressful and thereby continuing the feed-forward nature of the cascade."

Measures of Anxiety and Emotion

In addition to subjective measures of anxiety, heart rate is a widely used measure of physiological response. Heart rate acceleration has been observed when subjects are asked to imagine participating in fear-provoking scenes (Bauer and Craighead, 1979). Bradley et al. (1993) and Greenwald et al. (1989) showed that unpleasant slides tend to be associated with greater cardiac deceleration. This difference between the two findings (heart rate acceleration with fearful imagery and heart rate deceleration with unpleasant slides) demonstrates that because of its great sensitivity to attentional and response factor, heart rate performs poorly as a reliable measure of emotional state (Bauer 1998). Unlike skin conductance, the direction and pattern of heart rate changes depend to a large extent on the nature of the stimulus and the manner in which the individual interacts with task demands. For the present study, we will monitor heart rate with a pulse sensor.

Emotional judgments can be standardized and assessed using a simple dimensional view which assumes emotion can be defined as a coincidence of values on a number of different strategic dimensions (Lang et al. 1997). Osgood et. al (1957) founded the view in which factor analyses conducted on a wide variety of verbal judgments indicated that the variance in emotional assessments were accounted for by three major dimensions: two primary dimensions of affective valence (pleasant to unpleasant) and arousal (calm to excited) and a third dimension of dominance or control. Lang (1980) devised the Self-Assessment Manikin (SAM), an affective rating system to asses the three dimensions of pleasure, arousal and dominance. A graphic figure is used to depict each of the three dimensions to indicate emotional reactions. The valance dimension (Appendix A, 1) consists of 5 figures which range from a smiling, happy figure to a frowning, unhappy figure. The arousal dimension (Appendix A, 2) represents arousal (likened to the sensation elicited by running up a flight of stairs) caused by chest pressure, ranging from absolutely no chest pressure and arousal to maximum chest pressure and arousal. The third dimension of dominance or control is represented with a large figure (total control) to a small figure (dominated).

Aversive Respiratory Stimuli

A mechanism that may underlie the link between overperception of dyspnea and anxiety is interoceptive conditioning, a learning process by which initially neutral, low-level interoceptive (respiratory) sensations become predictive for subsequent dyspnea and anxiety (US, unconditioned stimulus). The extent to which the degree of airway pathology corresponds with self-reported symptoms varies strongly among pulmonary patients. For example, some patients hardly notice significant changes in respiratory functioning ("underperceivers"), while others report symptoms in excess of physiological abnormalities ("overperceivers") (Nguyen et al, 1996). The latter group is characterized by excessive medication intake, unwarranted illness behavior and hospitalization (Put et al, 1999; Put et al, 2000). Within the two-dimensional affective space of emotions (Lang, Bradley & Cuthbert, 1990) respiration covaries particularly with arousal. Nyklicek, Thayer and Van Doornen (1997) found that emotions can be discriminated most successfully by the respiratory component, which is related to the arousal dimension.

Inhalation of 20% CO_2 has been used previously as a US in fear conditioning studies in a normal population (Forsyth, 1998). In addition to the more traditionally used CO_2 stimulus, preliminary studies in this laboratory have shown that inspiratory loads are aversive. Using a differential conditioning paradigm, we tested whether interoceptive hypercapnic conditioning could be established in healthy subjects. An increased pressure on the upper arm (40 mmHg) served as conditional stimuli (CSs); a 20 s inhalation of 20% CO_2 enriched air and an inspiratory resistive load (15 cmH20) served as unconditional stimuli (US). Both the training and the extinction phase consisted of 3 CS+ and 3 CS- presentations (semi-randomized). SCR, EEG, pulse rate, $FETCO_2$, mouth pressure, airflow and tidal volume were recorded during stimulus presentations. Following each trial, participants rated the trial on 3 emotional dimensions of pleasantness, arousal and dominance. Subjects also rated fear, breathlessness and other panic symptoms experienced after each stimulus presentation. The subjective rating results indicate that the inspiratory resistive load and CO_2 inhalation were equally aversive. The inspiratory load elicited greater breathlessness than CO_2 inhalation. Both load and CO_2 independently elicit panic symptoms. These results suggest that both CO_2 inhalation and inspiratory loads elicit aversive subjective sensations. These results further suggest that loads can be used to investigate panic symptoms.

Van De Bergh et al. (1995) established a respiratory learning model in a Pavlovian conditioning paradigm and analyzed the relationship between respiratory responses and somatic complaints during acquisition and test. Occasional reductions in carbon dioxide may cause both somatic responses that underlie subjective complaints and subsequently increases in negative affectivity that then lower the perceptual threshold for variations in somatic responses.

Aversive respiratory stimuli may increase an introspective, apprehensive, negativistic and vigilant perceptual/ attentional focus to their bodies which may lower the perceptual threshold for somatic sensation (Van De Bergh et. al., 1995). Likewise, it is conceivable that altering the breathing dimensions by applying extended loads will cause somatic responses which will in turn increase negative affectivity, lowering the perceptual threshold for breathing.

The aversive subjective sensations induced during our CO_2 conditioning studies suggest the need for further investigation of the unpleasantness of inspiratory resistive loads. These preliminary results are consistent with studies demonstrating that patients affected by chronic obstructive pulmonary disease are more likely to have depression and anxiety. This suggests that altered and disrupted breathing is not only unpleasant, but induces fear and altered perception of the true respiratory state.

It is hypothesized that sustained presentation of resistive loads above 15 $cmH_2O/l*sec^{-1}$, will increase negative affectivity as load duration increases, resulting in increased magnitude estimation and subjective symptom expression.

CHAPTER 2
PERCEPTION OF MULTIPLE BREATH RESISTIVE LOADS

Introduction

A patient's emotional reaction to a sense of breathlessness exacerbates their perception of breathlessness (Bailey et al., 2004).The extent to which the degree of airway pathology corresponds with self-reported symptoms varies strongly among pulmonary patients. For example, some patients hardly notice significant changes in respiratory functioning ("underperceivers"), while others report symptoms in excess of physiological abnormalities ("overperceivers") (Woods et. al., 2003). The latter group is characterized by excessive medication intake, unwarranted illness behavior and hospitalization (Put et al., 1999; Put et al., 2000).

The respiratory mechanical load to breathing is increased in most pulmonary diseases. Asthma is a common pulmonary disease that is associated with increases in respiratory resistance and decreased respiratory compliance. This increases the mechanical load to breathing. An asthma attack is characterized by a transient, episodic increased resistance and decreased compliance that is sustained for minutes to hours. This means that the patient must make multiple inspiratory efforts against an increased load related to the bronchoconstriction. The patient initially experiences a "single-breath" type of load but then progresses to experience a multiple-breath load application. This is one reason why single-breath loading only partially simulates the sensations related to an asthmatic attack (Buki et. al., 1987). There has never been a systematic investigation of the perception of increased resistance when applied for multiple breaths, which is a closer representation of naturally occurring transient airway obstructive event such as an asthma attack. Further, previous studies have shown decreased sensitivity to increased mechanical loads in asthmatic subjects, but only using relatively small loads (up to 8

$cmH_2O/l*sec^{-1}$) (Bonnel et al.,1987). Adults admitted into the hospital with asthma are significantly more likely to be female (Woods et al., 2003; Senthilselvan et al., 1995; Hyndman et al., 1956; Wilkins et al., 1993;, Rao et. al., 2003). Measures of asthma morbidity have been shown to be disproportionately higher in females (Woods et al., 2003) and there is a higher trend for female readmission (Chen et al., 2003).

Ventilation of the lung is a mechanical process. The respiratory muscles act as a pump to generate the driving force for air to flow and increase the lung volume. Application of extrinsic mechanical loads of sufficient magnitude will alter this mechanical process and lead to a conscious awareness of the loads (Wiley et al., 1966; Noble et al.,1972; Campbell et al.,1961; Buki et al., 1983; Wiley et al., 1966). Respiratory load perception is commonly studied using only single breath load application (Wiley et al., 1966). The inspiratory load is applied for a single breath and there are 2-6 unloaded breaths before another load is applied. Studies of background loading have used small resistive loads (<8 $cmH_2O/l*sec^{-1}$) applied continuously (Wiley et al., 1966). Subjects usually accommodate to the background load (Ro) and do not report perception of the background within 2-3 minutes. It is also known that an elevated background load increases the threshold for resistive load detection (Bennett et al., 1962). The perception of respiratory mechanical events is dependent on two processes. The first is load detection, which has been studied by using difference threshold methods (Campbell et al., 1961; Wiley et al., 1966; Buki et al., 1983). The magnitude that elicits detection of 50% of the stimulus presentations is defined as the detection threshold. The load-detection threshold has been shown to be a constant fraction of the background load intrinsic to the respiratory apparatus and the subject (Wiley et al., 1966). Hence, an increased background load will require a greater added load for detection to occur. The second perceptual process is cognitive evaluation of the load.

This includes differentiation of the load type and accompanying estimation of the load magnitude (ME). Subjects are usually presented a single breath load and required to provide an estimate of the sensory magnitude of a supra-detection-threshold load using a numerical scale such as the modified Borg scale, or cross-modality matching, such as handgrip tension sensation to match the magnitude of respiratory sensation. These studies show that the perceived estimate of the load magnitude is linearly related to the load magnitude when a log-log transformation is used. The slope of the line is a measure of the sensitivity of the subject to the stimulus. Again, these studies are done using only single-breath load presentations. We wanted to determine if the perception of an inspiratory load changes as a function of the number of continuous inspiratory efforts against the load.

With a small increase in sustained extrinsic resistance (Ro<5 $cmH_2O/l*sec^{-1}$), such as background loading used in previous load detection studies (Wiley et al., 1966), have reported that subjects accommodate to the load but did not investigate the perception of the increased, sustained background load, only load added to the background (Wiley et al., 1966). Higher load magnitudes have not been used as elevated extrinsic background loads so it is unknown if this accommodation occurs over the range of inspiratory resistance (5-50 $cmH_2O/l*sec^{-1}$) commonly reported with an asthma attack. We hypothesized that multiple breaths against a small (>15 $cmH_2O/l*sec^{-1}$) resistive load would result in a decreased perceived load magnitude as the number of inspiratory efforts increase (accommodation). We further hypothesized that increasing the resistance would increase the perceived load magnitude (amplification) with increased breath number for resistive loads greater than 15 $cmH_2O/l*sec^{-1}$. We tested these hypotheses using magnitude estimation of multiple breaths (10 breaths) against a range of inspiratory resistance (5-40 $cmH_2O/l*sec^{-1}$). We reasoned that if the perceived magnitude of the load decreased from breath 1 to breath 10, then the subject accommodated to the load. Conversely, if the subject estimated the load as greater on breath 10 than breath 1, then the subject amplified their perception of the load.

Methods and Materials

The study was approved by the University of Florida Institutional Review Board. Consent was obtained from each subject prior to the beginning of the study. The subjects were asked to refrain from strenuous physical activity, large meals and caffeine for at least four hours prior to the tests. The subject's intrinsic respiratory resistance was measured using the forced oscillation method, which utilizes sound waves to determine the airway resistance. The subjects were seated in front of the apparatus and breathed "normally" through the mouthpiece, with their cheeks supported by both of their hands. Approximately 10 tidal breaths were collected continuously to determine airway resistance (Jaeger Toennies, Medizintechnikmit System, V. 4.5). The test was repeated at least three times for each subject with a one-minute rest between repetitions. The average of three measures of the resistance at 5 Hz was used as the subject's respiratory system resistance.

Subjects were seated in a lounge chair in a sound isolated chamber separated from the experimenter and the experimental apparatus (Figure 2-1). The subject respired through a mouthpiece connected to a non-rebreathing valve with their nose clamped. The inspiratory port of the valve was connected to the resistive load manifold. The inspiratory airflow signal was displayed on the oscilloscope in front of the subject. Initially, the subject was asked to breathe normally with eyes closed. A line was placed on the oscilloscope screen that coincided with peak inspiratory flow rate with quiet breathing. This was the target flow rate. The subject opened their eyes and continued to breathe normally while watching the oscilloscope screen. They were instructed to have the peak of the airflow with each breath "hit" the target line during the entire experiment. The subjects were instructed that when the red light above the oscilloscope was illuminated, the next breath would be loaded. The light was illuminated during expiration, cueing the subject that the next 10 breaths had a load and they should breathe to their airflow target on each breath. A green light was illuminated on the 1st, 5th and 10th loaded breath cueing the subject to estimate their perceived magnitude of the load. They estimated the perceived load magnitude using a 0-10 modified Borg category scale according to how difficult it was to breathe-in.

A series of test loads was presented in a practice session to familiarize the subject with load sensation, the perception task and the range of loads. After practice, the subject was given a 5-minute rest. There were a total of 2 experimental sessions. During the experimental session, the subject listened to music of their choice, which masked experiment sounds. There were a total of 6 resistive load magnitudes: 5 $cmH_2O/l*sec^{-1}$, 10 $cmH_2O/l*sec^{-1}$, 15 $cmH_2O/l*sec^{-1}$, 20 $cmH_2O/l*sec^{-1}$, 30 $cmH_2O/l*sec^{-1}$, and 40 $cmH_2O/l*sec^{-1}$. Each load was presented for 10 consecutive breaths. At loaded breaths 1, 5, and 10, the subject provided a magnitude estimation of their difficulty of breathing. A minimum of a 10-breath period with unloaded breathing separated each load presentation to allow the subject to recover. The loads were presented in a randomized block design. A total of 3 presentations of each load were applied in the first experimental trial. A 5-minute break was given before repeating the load presentation protocol in the second experimental trial. This resulted in a total of 6 10-breath presentations of each load magnitude over 2 experimental trials. The subject was monitored by the experimenter with a video camera that did not record the subject's image.

Data Analysis: The Borg scores for breath 1, 5 and 10 for each individual subject were averaged for the 6 presentations of each load magnitudes. The averages were then grouped into a male group and female group by load magnitude. Three-way repeated measures analyses of variance were used to examine the effects of sex, load magnitude, and breath number on the magnitude estimation of the resistive load. If any 3-way ANOVA results indicated a significant main effect of training at $\alpha = 0.05$, then a t-test of dependent variables was performed. Statistical comparisons were conducted with Sigma Stat software, with a significance level of $p<0.05$. The dependent variables for breaths 1, 5, and 10 were averaged for each load magnitude trial. The results are presented in Table 2-1. A total of 13 subjects were tested for this study.

Results

The results of the 3-way ANOVA indicated that the main effect of load magnitude on load magnitude estimation ($F = 64.793$, $p< 0.001$). There was a significant effect of sex on breath number ($F = 4.379$, $p< 0.014$). There was no significant sex by load magnitude by breath number interaction ($F = 0.377$, $p=0.955$).

Overall, the group (Figure 2-2) did not change their magnitude estimation by breath number for resistive loads ranging from 5 $cmH_2O/l*sec^{-1}$ to 15 $cmH_2O/l*sec^{-1}$ but had a significant difference in magnitude estimation for breath number of 30 $cmH_2O/l*sec^{-1}$ and 40 $cmH_2O/l*sec^{-1}$. The ME response for breaths 1,5 and 10 for the combined subject groups, males and females is presented in Table 2-1.

There was no significant group difference between the ME for breath 1 and 10 for R loads of 5 $cmH_2O/l*sec^{-1}$, 10 $cmH_2O/l*sec^{-1}$, 15 $cmH_2O/l*sec^{-1}$, and 20 $cmH_2O/l*sec^{-1}$ but there was a significant group difference for large R loads of 30 $cmH_2O/l*sec^{-1}$ and 40 $cmH_2O/l*sec^{-1}$ (Table 2-1). For the male group, the average ME rating for the smallest resistive load (5 $cmH_2O/l*sec^{-1}$) for the first breath was not significantly different than the 10th breath. Similarly, the average ME rating for females for this load magnitude was not significantly different by the 10th breath (Figure 2-3). The ME for males did not change between breath 1 and 10 for the 5 $cmH_2O/l*sec^{-1}$, 10 $cmH_2O/l*sec^{-1}$, 15 $cmH_2O/l*sec^{-1}$, 20 $cmH_2O/l*sec^{-1}$ and 30 $cmH_2O/l*sec^{-1}$ load magnitudes, but decreased with the 40 $cmH_2O/l*sec^{-1}$ load (Table 2-1, Figure 2.3). The ME for the 5th and 10th breaths of the 20 $cmH_2O/l*sec^{-1}$, 30 $cmH_2O/l*sec^{-1}$ and 40 $cmH_2O/l*sec^{-1}$ R loads was greater than the 1st breath for females (Table 2-1, Figure 2-4). Males estimated the 40 $cmH_2O/l*sec^{-1}$ R load on the 1st breath the same as females but the ME on the 10th breath, the male ME for 40 $cmH_2O/l*sec^{-1}$ was significantly less than females. These results demonstrate that magnitude estimation of resistive loads greater than 15 $cmH_2O/l*sec^{-1}$ with a sustained 10-breath trial significantly increases in females, but either did not change or significantly decreased in males.

Discussion

The ventilatory response to added mechanical loads can be regarded as the sum of two components: one representing the effect of the passive respiratory system and one representing the effect of neural load-compensating mechanisms (Axen et al., 1982). Although the ventilatory response to loads is governed primarily by respiratory system mechanics and by reflexes, behavioral and cognitive factors play a role in this response as well (Hudgel et al., 1982; Tiller et al., 1987). Cognitive factors can modify a subject's load response by symptom amplification, or they may exhibit an exaggerated subjective response to a load. In the present experiment, all subjects are presented with the same types and sizes of loads, eliciting similar neural load-compensation reflexes. There was no significant group difference between the ME for breath 1 and 10 for R loads of 5 $cmH_2O/l*sec^{-1}$, 10 $cmH_2O/l*sec^{-1}$, 15 $cmH_2O/l*sec^{-1}$, and 20 $cmH_2O/l*sec^{-1}$ but there was a significant group difference for large R loads of 30 $cmH_2O/l*sec^{-1}$ and 45 $cmH_2O/l*sec^{-1}$. This indicates that subjects similarly perceive loads below 15 $cmH_2O/l*sec^{-1}$, and respond differently to large loads, 30 and 45 $cmH_2O/l*sec^{-1}$. These larger loads induce a psychophysiological response that may result in behavioral load compensation.

Subjects who exaggerate subjective responses tend to be more anxious, self-conscious and have low self esteem, and may be more likely to report other symptoms as well (Schwartz et al. 1978; Taylor 1953; Lipman 1969). Also, subjects with psychological characteristics such as anxiety or depression may demonstrate altered physiological and ventilatory responses to a load when compared to control groups. While the present study showed an increasein perception of loads greater than 20 $cmH_2O/l*sec^{-1}$ it remains unknown if the psychological state of the subjects was altered by sustained loaded breathing. Future studies are needed to include subjective measurements to determine psychological state related to sustained loaded breathing.

Axen (1984) reported that men actively prolong inspiration more than women during resistive loading, and women actively shorten inspiration more than men during inspiratory loading, although these differences do not reach statistical significance. The load-compensation behavior exhibited by men and women was similar and tidal volume responses to loading do not differ (Axen 1984). In addition to physiological differences, Axen (1984) suggested that men and women could perceive the same load differently, due to the fact that load detection capability depends critically on intrinsic impedance (Wiley 1966). Intrinsic impedance is due to mechanical properties of the subject's respiratory system. While the subjects in the current study had sex predicted normal pulmonary mechanics, there were respiratory mechanical differences between males and females. Thus, the results of the present study support the suggestion that men and women perceive the same load differently in part due to sex differences in respiratory mechanics.

Females tend to have a greater sensitivity to their perception of physical stimuli. As previously reviewed (Edwards 2003), females demonstrate significantly greater pain sensitivity for both experimental and clinical pain. Women with respiratory disorders such as COPD self-report more psychological distress than men ((Laurin 2007; Di Marco et al. 2006). Female patients are more disposed to anxiety that correlates well with the dyspneic component of chronic obstructive pulmonary disease (Di Marco et al. 2006). When females are affected by pulmonary disease, they report less confidence in their ability to control their respiratory symptoms and have less total and activity-related quality of life compared to men (Laurin 2007.) These sex-related predispositions and differences are consistent with thesustained loaded breathing magnitude estimation difference demonstrated in the present study.

The perception of altered respiratory function by women may be more sensitive but less specific than by men, and socio-cultural factors (what a patient feels is socially acceptable or expected) also play a role in the sex differences in the perception, reporting, and diagnostic interpretation of respiratory symptoms (Becklake and Knauffman, 1999). Psychological factors such as depression have also been linked to the reporting of respiratory symptoms, though sex differences in rates of reporting by psychological status have not been examined (Becklake and Knauffman, 1999). Further research is necessary to determine the psychological responses and differences in magnitude estimation of sustained inspiratory loads between the two sexes.

These results suggest that the difference between the ME for breath 1 and breath 10 may be a function of the change in ventilatory state and may reflect the induction of an affective component to the load sensation. It remains unknown what cognitive and emotional responses are induced during multiple-breath resistive loads. It is also unknown if specific subject groups are more susceptible to aversive respiratory stimuli. For this reason, we chose to extend this study to include ventilatory response and subjective measures of multiple breath resistive loads. These results lead us to our next study of the subjective and cognitive responses to sustained breath for multiple loads.

Table 2-1 The mean ME (±standard deviation) for males and females for each load magnitude and breath number. The * indicated significant difference ($p<0.05$) for ME between breath number for a load magnitude. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and breath number.

Group Load ($cmH_2O/l*sec^{-1}$)	Breath 1	Breath 5	Breath 10
R=5	1.5 (±0.9)	1.3 (±0.9)	1.4 (±0.9)
R=10	2.2 (±1.1)	2.3 (±1.3)	2.4 (±1.3)
R=15	3.1 (±1.4)	3.3 (±1.2)	3.3 (±1.6)
R=20	3.8 (±1.2)	4.4 (±1.2)	4.7 (±1.6)
R=30	4.9 (±1.6)	5.8 (±1.6)	5.9 (±1.4) *
R=40	6.1 (±2.1)	6.9 (±1.7)	6.9 (±2.0) *

Male Load ($cmH_2O/l*sec^{-1}$)	Breath 1	Breath 5	Breath 10
R=5	2.1 (±0.8)	1.7 (±0.8)	1.7 (±0.9)
R=10	2.6 (±1.0)	2.5 (±0.9)	2.6 (±1.1)
R=15	3.8 (±1.5)	3.4 (±1.4)	3.5 (±1.4)
R=20	4.1 (±1.3)	4.0 (±1.0)	4.1 (±1.1)
R=30	5.2 (±1.2)	5.5 (±1.0)	5.3 (±1.0)
R=40	6.7 (±1.5)	6.3 (±1.5)	5.6 (±1.5)*$^{\#}$

Female Load ($cmH_2O/l*sec^{-1}$)	Breath 1	Breath 5	Breath 10
R=5	1.1 (±0.6)	1.1 (±0.9)	1.3 (±0.8)
R=10	1.8 (±0.9)	2.0 (±1.4)	2.2 (±1.3)
R=15	2.9 (±0.7)	3.1 (±1.0)	3.1 (±1.6)
R=20	3.5 (±0.9)	4.7 (±1.2)*	5.1 (±1.7)*
R=30	4.7 (±1.7)	6.0 (±1.7)*	6.4 (±1.5)*
R=40	5.6 (±2.2)	7.0 (±1.9)*	7.4 (±1.9)*$^{\#}$

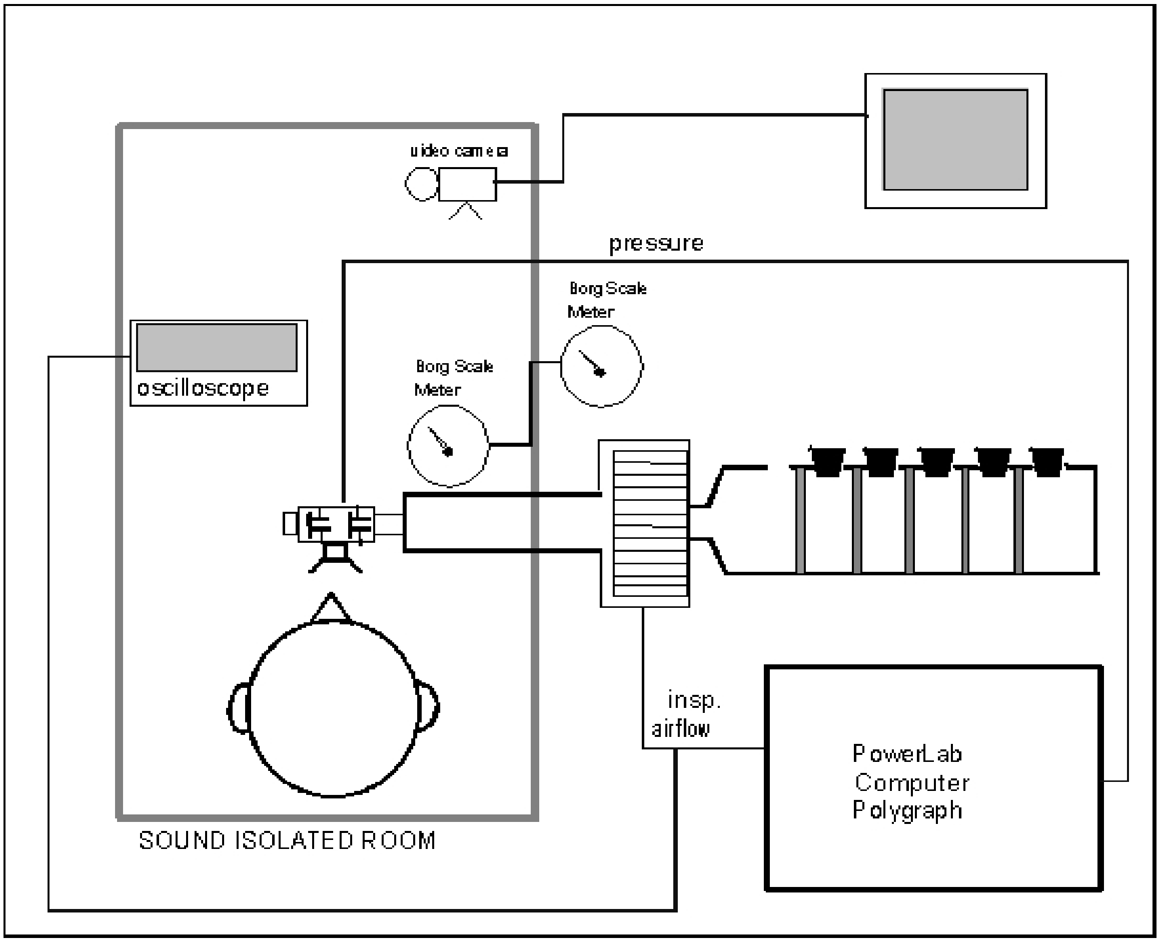


Figure 2 -1.Experimental set up for experiments 1 and 2. Subjects were seated in a sound isolated room and separated from the experiment to avoid any detection and observation of experimental manipulations by the subject. Their image was observed via video camera but not recorded, and the resistive manifold was attached to the mouthpiece.

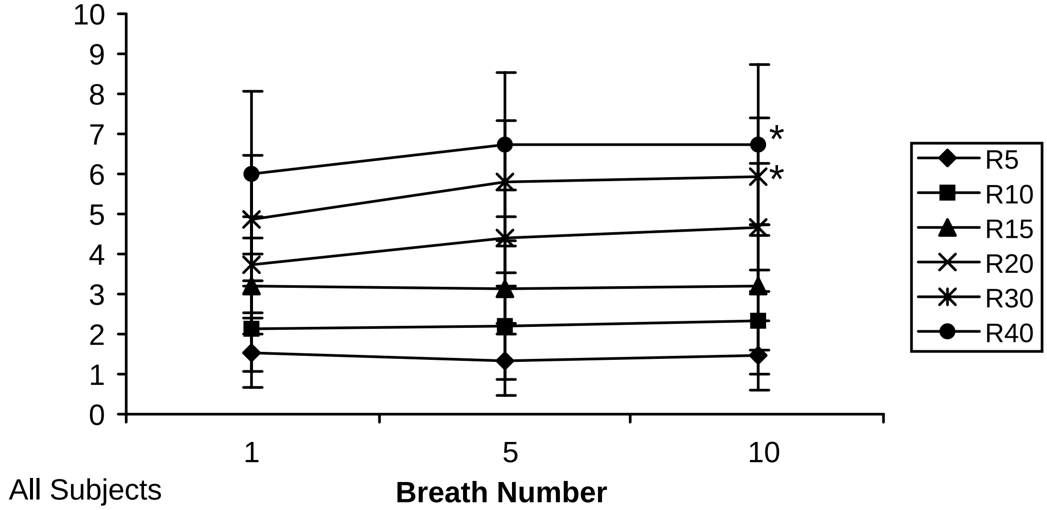


Figure 2-2. The mean (± standard deviation) ME scores of all subjects according to load magnitude and breath number. The vertical axis is the ME scores. The horizontal axis is the breath number the ME for each load magnitude was made. The * indicated significant difference ($p<0.05$) for ME between breath number for a load magnitude.

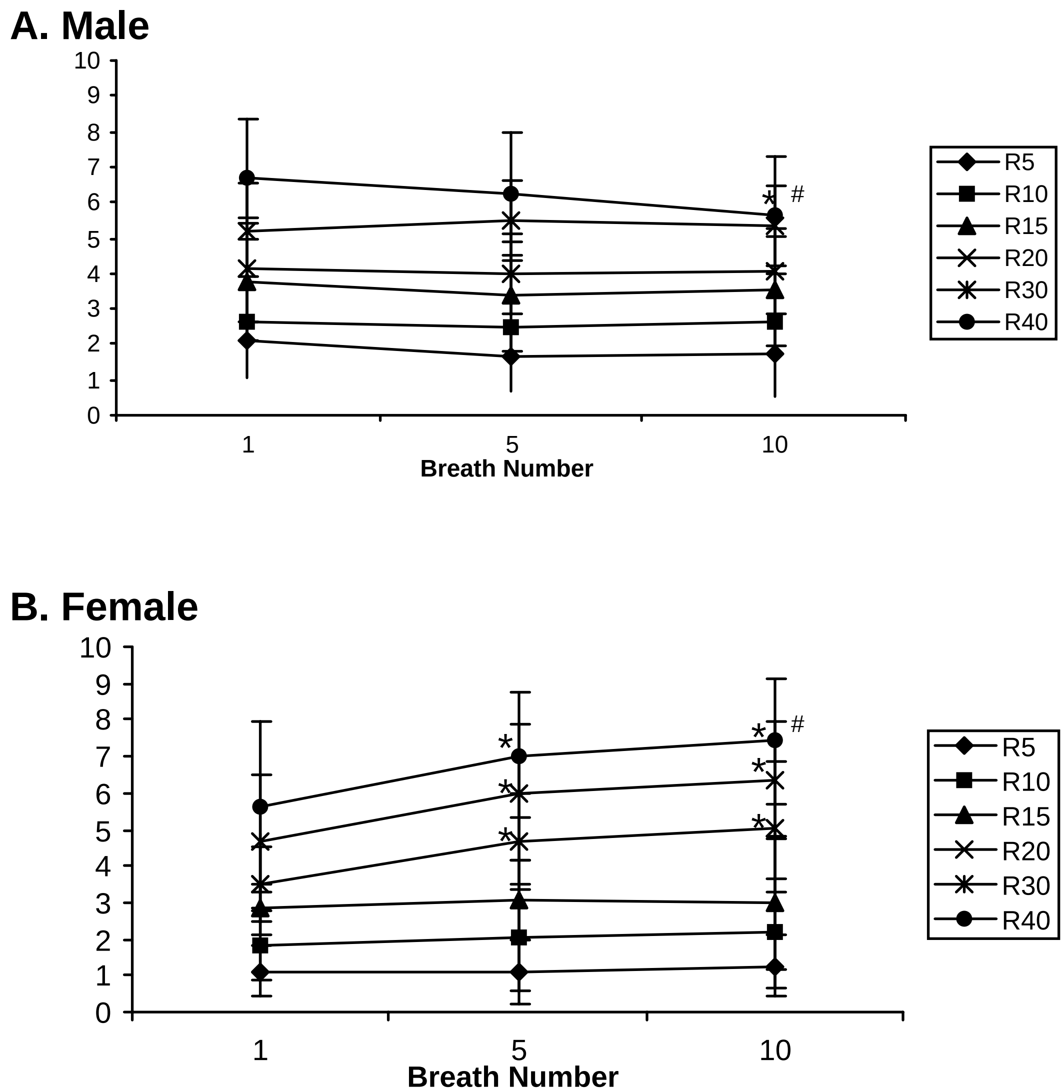


Figure 2-3. The mean (± standard deviation) ME scores of males and females according to load magnitude and breath number. The vertical axis is the ME scores. The horizontal axis is the breath number the ME for each load magnitude. A) The average ME scores for males. B) The average ME scores for females. The * indicated significant difference ($p<0.05$) for ME between breath number for a load magnitude. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and breath number.

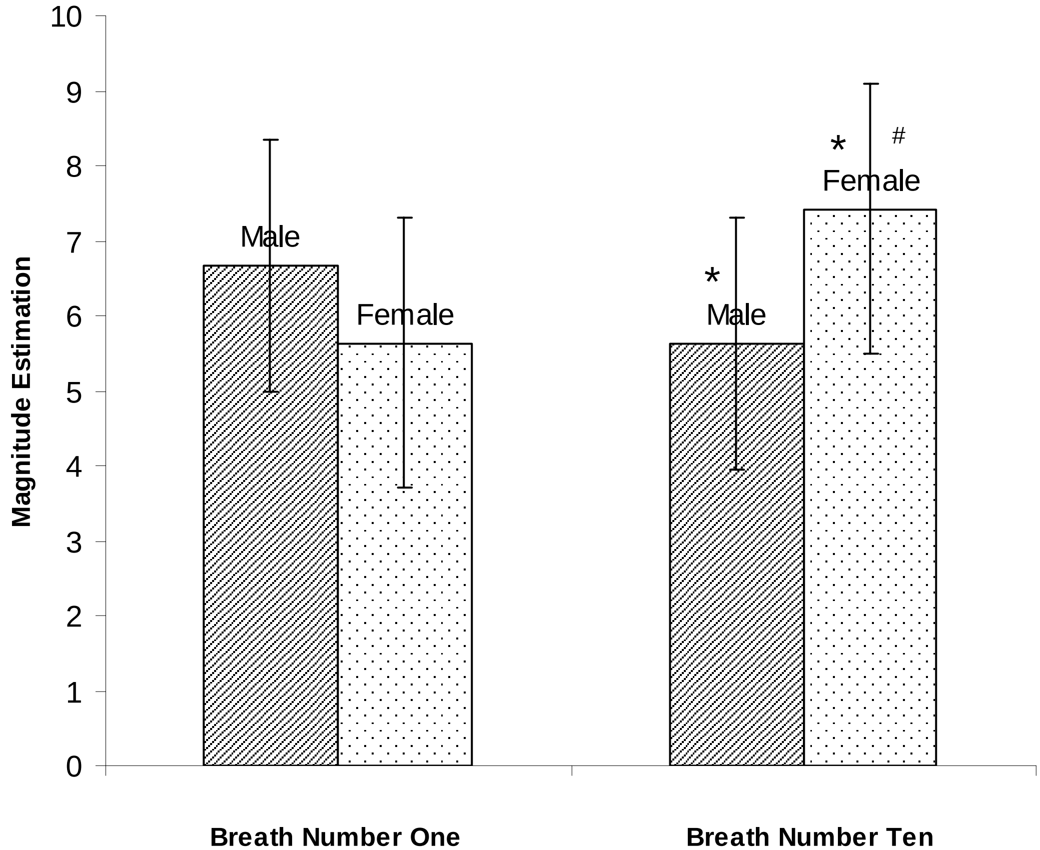


Figure 2-4. The mean (± standard deviation) ME for males and females on breath 1 and 10 for the 40 cmH_2O/L*sec^{-1} resistive load. The * indicated significant difference ($p<0.05$) for ME between breath number for a load magnitude. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and breath number.

CHAPTER 3
PERCEPTION AND SUBJECTIVE RATINGS OF 20-BREATH RESISTIVE LOADS IN MALES AND FEMALES

Introduction

Inspiratory loading has been used to study the perceptual mechanisms underlying and mediating respiratory mechanical sensation and perception. There are load related parameters mediating respiratory sensation, specifically, the mechanical effects on volume, airflow and pressure; perceptual changes, magnitude estimation and anxiety responses; changes in the central neural activity; and blood chemical changes. To fully analyze perceptual changes such as magnitude estimation and anxiety responses to inspiratory loads, it is necessary to analyze breathing pattern changes, perceptual reports, and subjective feelings associated with the inspiratory load changes.

Breathing is unique among autonomic nervous system functions in its easy susceptibility to both conscious and unconscious control (Sinha et al., 2000). Although breathing is not always consciously controlled, a brief thought of breathing or a disruption of normal breathing will cause immediate conscious awareness of respiration. Human fearful responses, like breathing, are also mediated by both conscious and unconscious processes (Sinha et al., 2000). Inter-individual psychological variables can be expected to modulate the perception of breathing and response to aversive respiratory loads. CO2 inhalation produces anxiety and frank panic in panic disorder patients more so than in controls (Sinha et. al, 2000). Our Preliminary Studies have demonstrated that a 15 cmH2O/lps inspiratory R load has equal measures of aversiveness to 20% CO2. (Miller abstract, 2006, 2007; Van Diest abstract, 2006). It is, however, unknown if ventilation against an increased inspiratory load elicits subjective aversive feelings.

Many of the chemical inductors of animal fearful responses that mimic panic attacks (caffeine, CRF, yohimbine, lactate and cholecystokinin) also stimulate respiration as well as produce somatically uncomfortable sensations (Sinha et al., 2000). During breathing, increases in respiratory rate or minute ventilation appear to correlate substantially with subjective anxiety (Sinha et al., 2000). During panic attacks, complaints of air hunger, dyspnea, and rapid breathing are common (Papp et. al, 1993). This leads us to the suggestion that respiration is directly linked to subjective feelings of anxiety and panic, and in turn, respiratory stimuli may be aversive.

Anxiety is most commonly used to describe an unpleasant emotional state or condition. An emotional state exists at a given moment in time and at a particular level of intensity. Anxiety states are characterized by subjective feelings of tension, apprehension, nervousness, and worry, and by activation or arousal of the autonomic nervous system. (Speilberger et al., 1966, 1972, 1976, 1979). Although these states may be transitory, they can recur when evoked by appropriate stimuli and may endure over time if the evoking conditions persist. Personality traits, on the other hand, are conceptualized by Campbell et al. (1963) as “acquired behavioral positions.” They dispose an individual to view the world in a particular way to manifest “object consistent” tendencies. Trait Anxiety refers to relatively stable individual differences in anxiety-proneness (STAIS Manual). It is the differences between people in the tendency to perceive stressful situations as dangerous or threatening and to respond to such situations with elevations of their state anxiety.

Emotional judgments can be standardized and assessed using a simple dimensional view which assumes emotion can be defined as a coincidence of values on a number of different strategic dimensions (Lang et al. 1997). Osgood et. al (1957) used factor analyses conducted on a wide variety of verbal judgments to indicate that the variance in emotional assessments were accounted for by three major dimensions: two primary dimensions of affective valence (pleasant to unpleasant) and arousal (calm to excited) and a third dimension of dominance or control. In 1980, Lang devised the Self-Assessment Manikin (SAM), an affective rating system to asses the three dimensions of pleasure, arousal and dominance. A graphic figure is used to depict each of the three dimensions to indicate emotional reactions. The valance dimension (Appendix A, 1-1) consists of 5 figures which range from a smiling, happy figure to a frowning, unhappy figure. The arousal dimension (Appendix A, 1-2) represents arousal (likened to the sensation elicited by running up a flight of stairs) caused by chest pressure, ranging from absolutely no chest pressure or arousal to maximum chest pressure and arousal. The third dimension (Appendix A, 1-3) of dominance or control is represented with a large figure ("dominating" or total control) to a small figure ("dominated" or total lack of control). The relationship of these emotional dimensions to load induced changes in breathing is, however, unknown.

Based on the results of study 1, which demonstrated a significant sex difference in response to sustained breathing against inspiratory loads, we incorporated the perception of extended loads with subjective measurements to determine the emotional effects of multiple-breath resistive loads in males and females. The extended load presentation was increased from 10 breaths to 20 breaths to allow the subject to adapt to, perceive, and discriminate/evaluate the load. A prolonged load presentation is more representative of respiratory disease states. We included a no-load presentation (R=0 cm H20/l/s) to control for apparatus or instructional effects. Golla and Antonovich (1929) reported that "any attempt to breathe through an open mouthpiece or mask, which is to say a piece of apparatus with centers the subject's attention on his breathing, invariably gives rise to an abnormal type of respiration." Examining the ventilatory pattern, subjective responses, and magnitude estimation of multiple breath resistive loads demonstrated the connection between objective and subjective responses to aversive respiratory stimuli. It was hypothesized that sustained resistive load presentations, above the threshold of 15 $cmH_2O/l*sec^{-1}$, will increase negative affectivity as load duration and magnitude increase, resulting in increased magnitude estimation and subjective estimations of fear of suffocation and sensations of dyspnea. It was further hypothesized the females would have greater negative affectivity than males. The following experiments test these hypotheses.

Methods and Materials

Subjects. A total of 22 subjects were tested for this experiment. The average subject information is listed in Table 3-5. All subjects were required to satisfy the inclusion and exclusion criteria. Subjects were required to be in good general heath with no significant medical history of neurological, cardiovascular, respiratory or any other major medical disorder. Subjects had to be free of any acute respiratory distress or, nasal congestion. The study was approved by the University of Florida Institutional Review Board. Consent was obtained from each subject prior to the beginning of the study. Subjects were divided into high and low negative affectivity (NA) participants, using a median split of the State-Trait-Anxiety-Index (STAI) scores (Van den Bergh et al., 1998). Three subjects were excluded from the final data inclusion for the following reasons: poor subject compliance, failure to self-report exclusion criteria (the subject was discovered to be a smoker after the experiment), and equipment failure. Subjects were required to comply with the study by answering each question and reporting load magnitude and subjective responses following each load presentation. Failure to respond to the experimenter's questions and evaluate loads resulted in exclusion of one subject due to poor compliance.

Experimental Protocol. The subjects were asked to refrain from strenuous physical activity, large meals and caffeine for at least four hours prior to the tests. Simple instructions were given to inform the subject how to complete the questionnaires, complete the pulmonary function test and breathe through the mouthpiece. A pulmonary function test (FVC, FEV1 and FEV1/FVC) recorded with forced expiratory maneuvers was performed. Subjects with less than 70% predicted

FEV1 and FVC were excluded from the experiment. All subjects met these criteria. The subject's intrinsic respiratory resistance was measured using the forced oscillation method. The subjects were seated in front of the apparatus and breathed "normally" through the mouthpiece, with their cheeks supported by both hands. Approximately 10 tidal breaths were collected continuously to analyze respiratory resistance by computer (Jaeger Toennies, Medizintechnikmit System, V. 4.5). The test was repeated at least three times for each subject with a one-minute rest between repetitions. The average of three measures of the resistance at 5 Hz was used as the subject's respiratory system resistance.

Subjects were seated in a lounge chair in a sound isolated chamber separated from the experimenter and the experimental apparatus (Fig. 3-1). Prior to load testing, each subject was given a The State Trait Anxiety Inventory (STAI), a 20-items questionnaire (Appendix A) measuring anxiety as a trait or as a state (Spielberger, C. D 1970). The STAI was repeated after the entire experiment was completed. The subject was then connected to the breathing apparatus and respired through a mouthpiece connected to a non-rebreathing valve with their nose clamped. The inspiratory port of the valve was connected to the resistive load manifold.

The subjects were informed that at any time during the experiment, they could remove the mouthpiece if they felt they could not breathe. They were also informed that at no time would they be at risk of injury due to lack of oxygen or airflow, and with proper effort, could always maintain constant ventilation. At no time were they informed of the specifics of the load magnitude.

Each subject was given a packet of the subjective responses prior to experimental trials. They followed along with the experimenter, who carefully explained each question, word meaning, and illustration. The subject was allowed to ask questions to clarify the meaning of the subjective responses. They were informed that the experimenter would give them a survey after each 20-

breath load presentation, for a total of 15 surveys. They demonstrated the ability to perform the task by completing a sample survey along with the experimenter.

The subjects were instructed that when the light in front of them was illuminated, the next breath would be loaded. They were also given a verbal cue, “Please rate your next breath using the magnitude estimation box.” This verbal cue was not changed, regardless of inspiratory load strength or individual subject. The verbal cue was given and light illuminated during expiration, cueing the subject that the next 20 breaths had a load and they would be estimating the magnitude of that upcoming load. A red light was illuminated on the 1st, 10th and 20th loaded breath cueing the subject to estimate their perceived magnitude of the load. They estimated the perceived load magnitude using a 0-10 modified Borg category scale (Borg 1982) according to how difficult it was to breathe against the inspired load.

A series of test loads was presented in a practice session to familiarize the subject with load sensation, the perception task and the range of loads. Initially, the subject was asked to breathe normally. After a minimum of five normal breaths, they were given an example of a “very small load” of 5 $cmH_2O/l*sec^{-1}$. Then they were given an example of a “large” load of 30 $cmH_2O/l*sec^{-1}$. They demonstrated proficiency and comprehension of the magnitude estimation by routinely pressing all buttons from 0-10. This also provided a reference for magnitude estimation results during data analysis. After practice, the subject was given a 5-minute rest. There were a total of 3 experimental sessions over a maximum of 3 hours. During the entire experiment, the subject listened to music of their choice, which masked experiment sounds. There were a total of 5 resistive load magnitudes: 0, 5 $cmH_2O/l*sec^{-1}$, 15 $cmH_2O/l*sec^{-1}$, 30 $cmH_2O/l*sec^{-1}$, and 45 $cmH_2O/l*sec^{-1}$. Each load was presented for 20 consecutive breaths, with the individual presentations separated by a minimum of 20 breaths. At loaded breath 1, 10, and 20, the subject provided a magnitude estimation of their perceived difficulty of breathing. The subject then had a breathing period with no loads presented to allow the subject to recover. The 5 load magnitudes were presented once in a randomized block design during the experimental trial. There were 3 trials with the 5 load magnitude presentation order independently randomized for each trial. A 5-minute break separated the experimental trials. This resulted in a total of three 20-breath presentations of each load magnitude over 3 experimental trials. The subject was monitored by the experimenter with a video camera that did not record the subject's image.

After each 20-breath resistive load presentation, the subject was given a 4 page packet to enter their subjective responses (Appendix B). They were asked to rate the following:

- Fear of suffocation on a 0-10 modified Borg scale (Borg 1982)
- General level of fear on a 0-10 modified Borg scale (Borg 1982)
- SAM Ratings: The subject can select any of the 5 figures comprising each scale, resulting in a 5-point scale for each dimension. Ratings are scored so that 5 represents a high rating on each dimension (high displeasure, high arousal, high dominance) and 1 represents a low rating on each dimension (low displeasure, low arousal, and low dominance).
- Body Sensation Questionnaire: The Diagnostic Symptoms Questionnaire (DSQ; Rapee et al., 1992) is a 15-item measure of the presence and intensity of 12 somatic and three cognitive DSM-III-R (American Psychiatric Association, 1987) panic symptoms. Intensity ratings for each endorsed symptom are made on a 4 point Likert-type scale (0 = not at all to 4 = very strongly felt). A Likert-type scale presents a set of attitude statements. The following composite measures can be derived from the DSQ: total number of physical symptoms and catastrophic and noncatastrophic thought, mean intensity of physical sensations, cognitive symptoms and reported fear.

Data Analysis

The Borg scores for breath 1, 10 and 20 for each individual subject were averaged for each load magnitude and trial. The averages were then grouped into a male group and female group.

Statistical comparisons were conducted with SigmaStat and SPSS software. Three-way repeated measures analyses of variance were used to examine the effects of sex, load magnitude, and breath number on the ME of the resistive load. If any 3-way ANOVA results indicated a significant main effect of training at $\alpha = 0.05$, then a t-test of dependent variables was performed. Statistical analysis of the magnitude estimation was done by blinding the analyst to the sex to avoid any bias during data analysis. Differences between groups were evaluated for ventilatory, ME and subjective measures, with a significance level of $p<0.05$. Ventilatory pattern was examined using Powerlab software, Excel, and SigmaStat. All 20 breaths of inspiratory resistive-loaded trial were selected for each subject in PowerLab software, then translated into quantitative numerical correlates using Excel. Mouth pressure, inspiratory time, and maximum airflow were selected along with the subject's self-reported magnitude estimation. A total of 60 breaths from all 3 trials for each load were selected for each subject, resulting in a total of 300 loaded breaths per subject. Breaths 1, 10, and 20 were averaged for each load magnitude trial. The loaded breaths were binned or analyzed separately by load magnitude, trial number and sex before being analyzed in SigmaStat. A 3-way ANOVA of breathing pattern was done for sex, load magnitude and breath number for dependent variables airflow, inspiratory time and mouth pressure. The results are presented in Table 3-1.

The subject estimated the load magnitude for each load at breaths 1, 10, and 20. The magnitude estimations were averaged across trials, then analyzed using SigmaStat with a 3- way repeated measures ANOVA for sex, load magnitude and breath number. All pairwise multiple comparisons were made using the Holm-Sidak method.

Subjective measures were self-reported after each 20-breath presentation of each load magnitude for a total of 15 subjective reports (4 pages each). These results were transferred into SPSS and grouped by sex, load magnitude and breath number for each symptom estimate, then analyzed using a 3-way ANOVA. Post-hoc analysis for ANOVA was performed using the Holm-Sidak method.

Results

Ventilatory response: Breath number between load magnitudes were compared for each load (R=0 $cmH_2O/l*sec^{-1}$, 5 $cmH_2O/l*sec^{-1}$, 15 $cmH_2O/l*sec^{-1}$, 30 $cmH_2O/l*sec^{-1}$ and 45 $cmH_2O/l*sec^{-1}$) and breath 1, 10, and 20. Non-similar breath numbers across load magnitude were not compared (i.e. breath 10, R=5 $cmH_2O/l*sec^{-1}$ with breath 20, R=15 $cmH_2O/l*sec^{-1}$). There was a significant effect of load magnitude on airflow, mouth pressure and inspiratory time. Importantly, for mouth pressure, airflow and time, there were no sex differences (Table 3-1). The group differences related to load magnitude are reflected in both males and females. Table 3-1 demonstrates the lack of significance between sexes for airflow, and table 3-2 demonstrates the lack of significant difference between sexes for time. The greatest difference in time and airflow is seen between the smallest of resistances (R=5$cmH_2O/l*sec^{-1}$) and the largest of resistances (R=45 $cmH_2O/l*sec^{-1}$) and is demonstrated in Figures 3-2 and 3-3. There is a linear increase in time and decrease in airflow as a function of load magnitude. Inspiratory time (Ti) lengthens as load magnitude increases and airflow decreases as load magnitude increases.

Magnitude estimation: A three-way repeated-measures ANOVA showed main effects for sex, load magnitude and magnitude estimation of the load (table 3-3). The effects of load magnitude and sex, as well as load duration, were found to be significant in subject's magnitude estimation of the load (Figures 3-4, 3-5, and 3-6). Load R=30 $cmH_2O/l*sec^{-1}$ and R=45 $cmH_2O/l*sec^{-1}$ were found to have significant differences for breaths 10 and 20 between males and females. For R= 15 $cmH_2O/l*sec^{-1}$, the magnitude estimation was significantly different for breath 20 between groups. Within sexes, the male group had an overall decreasing magnitude estimation trend for R= 15, 30, and 45 $cmH_2O/l*sec^{-1}$, between breaths 1 and 20 (Figures 3-4, 3-5, and 3-6). Although females demonstrated no significant difference between breaths 1 and 20 within their group, the figures in the ME data (Figures 3-4, 3-5, and 3-6) demonstrate a trend to increase in the ME for all load magnitudes with ME p=0.06 for R 45 $cmH_2O/l*sec^{-1}$ between breath 1 and 20.

The log-log slopes (table 3-4) were analyzed with a repeated-measure ANOVA, and also demonstrated main effects for sex, load magnitude and magnitude estimation of the load (Figure 3-6). Although breath 1 of R=45 $cmH_2O/l*sec^{-1}$ was not found to be significantly different, breaths 10 and 20 demonstrated group significant differences. Significant differences were found for the ME of all loads between breaths 1 and 20, demonstrating an alteration in perception of each load after sustained presentation of load. Female subjects had a lower slope indicating a compression of the perceptual score range. Females on breath 20 had a higher R5 score than males (they rated the smallest load greater than the males). Female ME slope decreases and male slope increases at breath 20 (figure 3-4, bar graph for slopes), because females compressed all their magnitude estimation into the higher score range.

Subjective responses: A 3-way ANOVA showed main effects for sex (F= 121.299, p<0.001), load magnitude (F=100.976, p<0.001) and breath number (F=137.515, p<0.001) to the subjective response. There was a significant interaction between sex and load (F= 12.469, p<0.001), sex and symptom magnitude estimation (F=2.764, p<0.001) and load and symptom magnitude estimation (F=5.738, p<0.001). These results are presented in tables 3-6 and 3-7 and Figure 3-7. As a group, load levels resulted in subjective increases in fear, fear of suffocation, distress, arousal due to chest compression, faintness, dizziness, trembling, and dyspnea. There were significant sex differences for the following subjective responses: fear, fear of suffocation, happiness, arousal due to chest compression, fear of losing control, faintness, dizziness, trembling and tingling. There were no significant group differences for sense of control, dyspnea, and palpations.

A repeated-measures ANOVA showed non-significant effects for sex in the mean scores of the State-Trait Anxiety Index (STAI) for subjects pre-experiment and post-experiment. Kruskal-Wallis One Way Analysis of Variance on Ranks of the delta-scores of the difference pre- and post-experiment did demonstrate significant differences for men in trait anxiety post experiment. A multiple pairwise comparison's procedure (Dunn's method) was used. Females had no significant change. These results are demonstrated in table 3-8 and Figures 3-9 and 3-10.

Discussion

Human subjects can easily detect and scale respiratory mechanical loads (Kelsen 1982, Kifle 1997; Killian 1981; Lansing 1996; Bijl-Hofland 2000; Taguchi 1991; Burki 1984; Burki 1983; Burki 1978; Bennett 1962). The respiratory load detection threshold is a psychophysical measure of respiratory sensation (Zechman 1986). Respiratory perception is a result of the physical awareness (what is sensed) and affective judgment (how it feels). Respiratory perception with added inspiratory resistive loads follows Stevens' psychophysical power law (Burki 1980; Gottfried S 1981; Killian 1982; Killian 1981; Wiley 1978). Consequently, perceived magnitude (ψ) of a stimulus is related to the physical magnitude of the stimulus (φ) by a constant (k) and an exponent (n): $\psi = k\, \varphi^{n}$. Most load perception studies have examined the perception of single breath resistive loads. This is the first study to combine behavioral measures, ventilatory analysis, and magnitude estimation with multiple breath resistive loads. These results demonstrate that the difference between the ME for breath 1 and breath 20 is a function of sex, the change in ventilatory state from breath 1 to 20, and reflects the induction of an affective component to the load sensation. The results of the present study demonstrate that the affective responses indicate that prolonged breathing against respiratory loads of moderate to high magnitude are aversive and cause negative affect.

Ventilatory response: The ventilatory response to added mechanical loads can be regarded as the sum of two components: one representing the effect of the passive respiratory system and one representing the effect of neural load-compensating mechanisms (Axen 1982). The load compensating component represents the action of neural mechanisms that modify the pressure developed by loaded respiratory muscles (Zhao et al. 2002). In conscious humans, repeated mechanical loading activates neural load-compensating mechanisms. The range of the neural adjustment varies with both load size and type, and is mainly a non-chemical stimulus initiating this behavior (Axen 1983).

The present study demonstrated that, for airflow and time, there are no sex differences in breathing pattern. This finding agrees with previous studies examining the sex-related ventilatory response to multiple breath resistive loads (Axen 1983; Axen 1984). Tidal volume responses do not differ between sex, and the combined group response to sustained loads is qualitatively similar. The present study extended this by identifying group differences related to load magnitude reflected in both males and females. Table 3-1 demonstrates the lack of significance between sexes for airflow, and Table 3-2 demonstrates the lack of significant difference between sexes for time. Hence, both sexes exhibit similar load compensation ventilatory responses to sustained breathing against resistive loads.

Adding resistive loads (ΔR's) to respiration changes airflow, volume, and pressure and the magnitude of the external load determines the degree of change (Kellerman 1999). The greatest load dependent difference in time and airflow is seen in between the smallest of resistances (R=5 $cmH_2O/l*sec^{-1}$) and the largest of resistances (R=45 $cmH_2O/l*sec^{-1}$). The inspiratory time is prolonged to allow for the decreased airflow to fill the lung to the same or greater tidal volume, maintaining alveolar ventilation. The change in time and airflow is a linear function of load magnitude. As the load magnitude increases, inspiratory time lengthens and airflow decreases. This load compensation modulation of breathing pattern is sustained over the entire 20-breath trial.

Magnitude estimation: The cerebral cortex is a significant component of the neural system processing sensory information related to mechanical effort and pattern of respiration. Consequently, the cerebral cortex is one neural component mediating the magnitude estimation of a load applied to breathing. The estimation of a magnitude of a load, along with initial detection of that load, is mediated by cortical processes, presumably within primary somatosensory and association areas (Webster, 2000). Human subjects are consciously aware of breathing against mechanical loads, and can easily discriminate the presence and type of respiratory mechanical loads, estimate the size of the loads and scale these respiratory mechanical stimuli (Williams et al., 1988). As increasing resistance opposes the respiratory pump, magnitude estimation of the applied respiratory load increases proportionally to the magnitude of the ΔR. This was evident in the present study, as load magnitude increased, magnitude estimation increased accordingly (Table 3-5). Ti increased and airflow decreased along with load magnitude.

Davenport et al.,(1991) used an animal model to examine detection of inspiratory loads in dogs. A tracheal stoma was used to eliminate the upper airway and tracheal receptors as sources of afferent input. Chemoreceptors were also eliminated as an input, because blood gases did not change. Davenport et. al. (1991) concluded that respiratory muscles are the most likely site for afferent information related to load detection. The animal results are consistent with load magnitude estimation with douoble-lung transplant patients (Zhao et al., 2003) and load elicited cortical activity in tracheostomized patients (Davenport, et al., 2006). They suggested that the respiratory pump muscle afferents mediate the sensory response to load compensation and the mechanisms mediating load detection and magnitude estimation are different. Our results in the present study support this hypothesis, demonstrated by the differing magnitude estimations of identical loads with similar breathing patterns between sex groups.

Magnitude estimation of inspiratory loads can be expressed in relation to magnitude of inspiratory pressure (Redline et al. 1991) This relationship can be attributed to the efferent command driving the respiratory system and magnitude estimation may be centrally mediated. The perceived magnitude of a load is linearly related to the added load when a log-log transformation is used. The slope of this relationship is an index of the perceptual sensitivity for the type of load presented. A numerically low slope value is indicative of poor perception sensitivity (Julius et al., 2002). A high slope is indicative of increased perception sensitivity. The log-log slopes (table 3-4) demonstrated main effects for sex, load magnitude and magnitude estimation of the load (Figure 3-6). Although breath 1 of R=45 $cmH_2O/l*sec^{-1}$ was not found to be significantly different, breaths 10 and 20 demonstrated significant group differences. Significant differences were found for the ME of loads between breaths 1 and 20, demonstrating an alteration in perception of each load after sustained presentation of load. Female subjects had a lower slope indicating a compression of the perceptual score range. Female slope decreases and male slope increases at breath 20 (figure 3-4, bar graph for slopes), because females had a greater ME of R5 on breath 20 that compressed their magnitude estimation into the higher score range. Males had a significant decrease in the magnitude estimation between breaths 1 and 20 in the opposite direction of the females. This provides evidence for a sex effect with males desensitizing with increasing breath number and females sensitizing with increasing breath number.

Subjective responses: Respiratory perception is a 2-stage process. Stage 1 is the discriminative dimension and includes the awareness of the spatial, temporal and intensity components of the respiratory disruption. In this stage, respiratory somatosensation generated by the discriminative awareness of respiratory stimuli is determined by the interaction between multiple respiratory afferent groups and brainstem respiratory motor drive. The second stage, the affective state, is a potentially important but little explored aspect of respiratory sensory processing. Within the two-dimensional affective space of emotions (Lang, Bradley & Cuthbert, 1990) respiration covaries particularly with arousal. Nyklicek, Thayer and Van Doornen (1997) found that emotions can be discriminated most successfully by the respiratory component, which is related to the arousal dimension. Subsequent to initial somatosensation, respiratory stimuli can evoke distress and motivate cognitive behavior. It has been previously shown that stress and anxiety is related to the over perception of respiratory symptoms, but the mechanism behind this connection is unclear (Put, 1999; Put, 2000). It is possible that distressing respiratory sensations may condition human subjects to have a heightened awareness of their breathing and may even induce respiratory related anxiety.

Ventilation is controlled primarily by respiratory system mechanics, arterial blood gases and neural reflexes. However, behavioral and cognitive factors also play a significant role in ventilatory neural response to loads (Hudgel 1982; Tiller 1987). Cognitive factors can modify a subject's load response by symptom amplification, or they may exhibit an exaggerated subjective response to a load. Subjects who exaggerate subjective responses tend to be more anxious, self-conscious and have low self esteem, and may be more likely to report other symptoms as well (Schwartz et al. 1978; Taylor 1953; Lipman 1969). Also, subjects with anxiety or depression may demonstrate altered physiological or ventilatory responses to a load when compared to control groups. Differences in the perception associated with loading between subjects and groups reflect differences in the subjective responses to loads.

Some subject groups, such as life-threatening asthmatics, have a unique decreased perceptual reactivity to resistive loads, which cannot be explained by differences in respiratory effort, airway mechanics, or task performance ability (Kifle, Seng & Davenport, 1997; Kikuchi et al., 1994). These patients have a unique perceptual processing deficit to respiratory loads and were predominantly males. Webster and Colrain (2000) reported that this deficit may be due to a problem in the transduction of afferent neural signals originating in muscle stretch receptors projecting to somatomotor cortical regions. Males in the present study demonstrated a perceptual decrease to sustained loads, which is evident by their decreasing magnitude estimation of the loads (figure 3-6). Further research is needed to determine if this male-related decrease in perception is due to a sex difference in the neural mechanisms mediating respiratory load perception.

It is possible that individuals with altered load perceptual sensitivity have an altered central neural threshold of respiratory perceptual gating. Sex differences in sensory gating can explain the altered subjective responses to load levels of 15, 30 and 45 for the sensation of fear, fear of suffocation, faintness and arousal. Females have a lower threshold for these respiratory sensations and symptoms, hence they express a greater than 0 response at a lower load than men. At the highest load (R=45 $cmH_2O/l*sec^{-1}$), the significant difference disappears because the males begin to express a positive number rating for the subjective sensations. Thus, the men have a higher threshold for these symptoms and when they are expressed, men have a lower average but eventually approach the symptom score of the females when the aversive respiratory stimuli gets large enough. The difference between male and female subjective symptom resistive load threshold may be due to differences in central neural gating.

Although there was no significant difference between groups for state anxiety scores, the delta scores for trait anxiety significantly decreased in males, and approached a significant increased in females. Trait anxiety implies differences between people in the disposition to respond to stressful situations with varying amounts of state anxiety. As a result differences of trait anxiety depends on the perception of a specific situation as psychologically dangerous or threatening, and depends on a person's past experience and background. High trait anxiety subjects exhibit state anxiety elevations more frequently because they tend to interpret a wider range of situations as dangerous or threatening. Trait anxiety scores are generally not influenced by stress and is relatively impervious to the conditions under which it has been given (Auerbach, 1973; Lamb, 1969; Spielberger et. al., 1973). This is seen in the male population who had a significant decrease in their trait anxiety, yet no increase in state anxiety.

A subject who associates a high degree of dyspnea with the introduction of a small inspiratory load to the airway can be considered a "symptom amplifier" (Laviette 2000). There was no group difference in the sensation of dyspnea, and dyspneic ratings increased linearly across both subject groups. Therefore, none of the subjects tested in this experiment were dyspnea symptom amplifiers, and their subjective results were representative of the respiratory aversiveness of the sustained inspiratory loads.

Individuals with high measures of state-trait anxiety have increased S2/S1 ratios with auditory and somatosensory stimulation suggesting reduced ability to gate-out some sensory stimuli (O'Donnell et al., 2007; Chou et al., 2007). This suggests that individuals with existing conditions of anxiety have an altered perceptual process, although this area needs to be examined in relation to respiratory sensation. Inducing anxiety-like responses with respiratory aversive stimuli also disrupts normal somatosensory perception in some subjects, as demonstrated by the magnitude estimation differences and differences in subjective responses.

Sex differences: The most likely source of the difference lies in the cognitive and emotional realm. Not only was there a lack of sex difference seen in physiological measurements, males and females changed their magnitude estimation scores in opposite directions. It is important to note that there was no sex difference in the first breath baseline magnitude estimation values, which represents the discriminative component of respiratory somatosensation. This indicates that during the course of 20 breaths of load presentation, the emotional component of respiratory perception was recruited by female subjects to enhance their perception of the load, resulting in a significantly different evaluation of the load.

Sex differences in the response and over-perception of symptoms are seen with many disease states. When patients are affected by pulmonary disease, women report less confidence in their ability to control their respiratory symptoms and have less total and activity-related quality of life compared to men (Laurin 2007). Female patients are more exposed to psychological impairment that correlates well with the dyspneic component of chronic obstructive pulmonary disease (Di Marco et al. 2006), which may correlate with the psychological changes demonstrated in the present study after prolonged breathing against inspiratory loads. Females tend to have a greater sensitivity to their perception of physical stimuli. Edwards (2003) demonstrated significantly greater pain sensitivity in females for both experimental and clinical pain. Females in the general population report a greater frequency, intensity and duration of pain-related symptoms than males (Edwards 2003). The perception of altered respiratory function by women may be more sensitive but less specific than by men (Becklake and Knauffman, 1999). Dyspnea is perceived as more important in women's quality of life scales than in men's (Jones 1992). Becklake and Knauffman (1999) also reported psychological factors such as depression have been linked to the reporting of respiratory symptoms, though sex differences in rates of reporting by psychological status have not been examined. This sex difference in respiratory symptom perception is supported by the sex related modulation of affective symptoms by resistive load in the present study.

Conclusion

In conclusion, this experiment demonstrates a significant sex difference in the perception, subjective ratings, and affective response to sustained inspiratory resistive loads. Sustained loads over 15 $cmH_2O/l*sec^{-1}$ elicit more negative affect responses in females, as demonstrated by increased ratings of fear, fear of suffocation, arousal, chest pressure, dizziness, fear of losing control, and sense of unreality. Sustained loads elicit sensations of dyspnea in both males and females, indicating that subjects do not adapt or accommodate their sense of dyspnea to large loads, but rather have to work harder to adjust to them. This is also evident in the ventilatory response of increasing airflow and time across both groups.

Table 3-1 The peak airflow for each resistive load magnitude, breath the ME was made and sex. There was there no significant difference between sexes for airflow.

	Female Airflow (L/sec)	Mean	Std Dev		Male Airflow (L/sec)	Mean	STD DEV	q Value	P
R=0	Breath 1	0.10	0.02	R=0	Breath 1	0.12	0.03	0.39	>0.05
	Breath 10	0.09	0.02		Breath 10	0.10	0.03	0.34	>0.05
	Breath 20	0.10	0.02		Breath 20	0.10	0.03	0.02	>0.05
R=5	Breath 1	0.10	0.02	R=5	Breath 1	0.13	0.07	Ns	>0.05
	Breath 10	0.09	0.02		Breath 10	0.10	0.04	Ns	>0.05
	Breath 20	0.09	0.02		Breath 20	0.11	0.05	Ns	>0.05
R=15	Breath 1	0.09	0.02	R=15	Breath 1	0.09	0.03	Ns	>0.05
	Breath 10	0.08	0.02		Breath 10	0.07	0.01	Ns	>0.05
	Breath 20	0.07	0.02		Breath 20	0.08	0.02	Ns	>0.05
R=30	Breath 1	0.08	0.02	R=30	Breath 1	0.07	0.02	Ns	>0.05
	Breath 10	0.07	0.02		Breath 10	0.06	0.02	Ns	>0.05
	Breath 20	0.07	0.02		Breath 20	0.07	0.02	Ns	>0.05
R=45	Breath 1	0.06	0.02	R=45	Breath 1	0.07	0.02	0.49	>0.05
	Breath 10	0.06	0.02		Breath 10	0.05	0.01	0.28	>0.05
	Breath 20	0.06	0.01		Breath 20	0.06	0.03	0.80	>0.05

Table 3-2 The inspiratory time for each resistive load magnitude, breath the ME was made and sex. There was no significant difference between sexes for inspiratory time.

	Female Time (sec)	Mean	STD DEV		Male Time (sec)	Mean	STD DEV	q Value	P
R=0	Breath 1	3.34	0.70	R=0	Breath 1	2.85	0.55	0.90	>0.05
	Breath 10	3.02	0.75		Breath 10	3.03	0.96	0.49	>0.05
	Breath 20	2.91	0.63		Breath 20	2.73	1.10	0.66	>0.05
R=5	Breath 1	3.87	0.84	R=5	Breath 1	3.29	0.98	Ns	>0.05
	Breath 10	3.58	0.63		Breath 10	3.29	0.62	Ns	>0.05
	Breath 20	3.67	0.61		Breath 20	2.68	0.81	Ns	>0.05
R=15	Breath 1	4.55	1.27	R=15	Breath 1	3.93	1.06	Ns	>0.05
	Breath 10	4.01	0.92		Breath 10	3.58	0.80	Ns	>0.05
	Breath 20	4.09	0.89		Breath 20	3.76	0.93	Ns	>0.05
R=30	Breath 1	4.85	1.14	R=30	Breath 1	4.24	1.16	Ns	>0.05
	Breath 10	3.97	1.31		Breath 10	4.02	1.19	Ns	>0.05
	Breath 20	4.16	0.99		Breath 20	4.26	1.10	Ns	>0.05
R=45	Breath 1	5.56	1.46	R=45	Breath 1	4.62	1.06	0.59	>0.05
	Breath 10	5.00	1.63		Breath 10	4.32	0.91	0.10	>0.05
	Breath 20	4.99	1.48		Breath 20	4.38	1.12	0.37	>0.05

Table 3-3 Mean magnitude estimation for each resistive loads at breath 1, 10, and 20 for males and females. The mean (± standard deviation) and corresponding p-values between load magnitude and between sex is presented when significantly different.

Female ME	Breath 1	Breath 10	Breath 20	t (M vs F)	P-value	P-value between sexes
R=0	0.08 (±0.16)	0.18 (±0.23)	0.18 (±0.20)	0.212		
R=5	1.37 (±1.18)	1.44 (±1.10)	1.47 (±1.14)	2.262		
R=15	3.35 (±1.54)	3.47 (±1.92)	3.48 (±1.90)	2.472		p<0.02 (Breath 10)
R=30	5.73 (±1.48)	6.1 (±1.39)	6.27 (±1.30)	5.981		p<0.005 (Breath 10) p<0.00006 (Breath 20)
R=45	6.37 (±1.98)	7.42 (±1.44)	7.62 (±7.78)	5.077	*p=0.06	p<0.005 (Breath 10) p<0.0001(Breath 20)
Male ME	**Breath 1**	**Breath 10**	**Breath 20**	**P-value**	**P-value**	**P-value between sexes**
R=0	0.02 (±0.05)	0.07 (±0.09)	0.17 (±0.17)	0.212		
R=5	1.37 (±0.95)	1.44 (±0.59)	1.47 (±0.26)	2.262		
R=15	3.19 (±0.81)	2.51 (±1.07)	2.34 (±0.65)	2.472	p<0.01	p<0.02 (Breath 10)
R=30	5.05 (±1.37)	4.18 (±1.36)	3.38 (±1.17)	5.981	p<0.009	p<0.005 (Breath 10) p<0.00006 (Breath 20)
R=45	6.49 (±1.37)	5.57 (±1.36)	4.68 (±1.17)	5.077	p<0.02	p<0.005 (Breath 10) p<0.0001(Breath 20)

Table 3-4 Mean (± standard deviation) log ME, log resistive load and log-log slope are presented for breath 1, 10, and 20, along with the corresponding between load p-values.

Female ME logs	Breath 1	Breath 10	Breath 20	P-val
R=0	0.62 (±0.28)	0.60 (±0.28)	0.57 (±0.24)	
R=5	0.03 (±0.42)	0.02 (±0.39)	0.10 (±0.37)	
R=15	0.49 (±0.18)	0.48 (±0.24)	0.47 (±0.27)	
R=30	0.75 (±0.11)	0.78 (±0.10)	0.79 (±0.10)	p<0.05
R=45	0.78 (±0.14)	0.86 (±0.09)	0.88 (±0.08)	p<0.05
ME Log-Log Slope	0.89 (±0.41)	0.91 (±0.39)	0.79 (±0.44)	p<0.05
Male ME logs	**Breath 1**	**Breath 10**	**Breath 20**	**P-val**
R=0	0.78 (±0.00)	0.78 (±0.00)	0.66 (±0.21)	
R=5	0.09 (±0.32)	0.23 (±0.28)	0.36 (±0.23)	p<0.05
R=15	0.49 (±0.13)	0.36 (±0.20)	0.35 (±0.15)	p<0.05
R=30	0.69 (±0.13)	0.60 (±0.14)	0.51 (±0.15)	p<0.05
R=45	0.80 (±0.10)	0.73 (±0.11)	0.66 (±0.12)	p<0.05
ME Log-Log Slope	0.94 (±0.34)	0.94 (±0.41)	1.05 (±0.30)	

Table 3-5 Mean (± standard deviation) subject demographic data for study 2.

	Male	Female
Age (yrs)	23.70 (± 3.4)	32.56 (± 10.81)
Weight (lbs)	170.10 (± 24.07)	143.22 (± 21.01)
Height (in)	70.55 (±3.01)	67.56 (±1.72)
	4.91 (± 0.45)	
FVC (liter)		4.17 (±0.13)
FVC % Pred	1.06 (± 0.16)	
Avg		0.85 (± 0.00)
	4.59 (± 0.31)	
FEV1 (liter)		3.35 (±0.62)
FEV1 % Pred		
Avg	1.11 (± 0.13)	1.27 (±0.00)

Table 3-6 Mean (± standard deviation) emotional subjective estimation responses to questionnaires. Significance between sexes is indicated by then asterisks.

Fear	Female	Male	F	*P= <.05
R=0	0.06(±0.19)	0(±0)	0.81	
R=5	0.15(±0.22)	0.04(±0.10)	1.87	
R=15	0.67(±0.57)	0.07(±0.20)	7.92	*
R=30	1.18(±1.07)	0.11(±0.15)	8.01	*
R=45	1.70(±1.77)	0.59(±0.51)	2.92	
Fear of Suffocation				
R=0	0.12(±0.31)	0(±0)	1.38	
R=5	0.58(±0.65)	0.30(±0.39)	1.28	
R=15	1.42(±0.75)	0.56(±0.58)	8.16	*
R=30	3(±1.40)	1.30(±1.20)	8.35	*
R=45	3.59(±1.45)	2.37(±1.31)	3.83	
Happiness				
R=0	1.4(±0.66)	1.41(±0.97)	0.00	
R=5	1.5(±0.71)	1.48(±0.96)	0.00	
R=15	2.13(±0.55)	1.52(±1.04)	2.67	
R=30	2.78(±0.74)	1.67(±0.99)	7.93	*
R=45	3.08(±0.80)	2(±1.09)	6.18	*
Sense of Control				
R=0	1.27(±0.64)	1.33(±0.78)	0.04	
R=5	1.4(±0.75)	1.41(±0.76)	0.00	
R=15	1.9(±0.79)	1.63(±0.90)	0.49	
R=30	2.4(±0.64)	1.82(±0.87)	2.83	
R=45	2.75(±0.69)	2.56(±0.83)	0.31	
Chest Pressure				
R=0	1.13(±0.32)	0.96(±0.11)	2.27	
R=5	1.4(±0.66)	1.11(±0.17)	1.61	
R=15	1.77(±0.74)	1.30(±0.51)	2.55	
R=30	2.32(±0.79)	1.48(±0.50)	7.39	*
R=45	2.68(±0.93)	2.11(±1.09)	1.47	

Table 3-7. Mean (± standard deviation) bodily subjective estimation responses to Diagnostic Symptom Questionnaire. Significance between sexes is indicated by the asterisks.

Dyspnea	Female	Male	F	*P= <.05
R=0	0.15(±0.31)	0(±0)	2.11	
R=5	0.38(±0.57)	0.19(±0.29)	0.85	
R=15	0.91(±0.75)	0.56(±0.60)	1.32	
R=30	1.36(±0.74)	0.96(±0.66)	1.61	
R=45	1.82(±0.94)	1.41(±0.93)	0.97	
Faintess				
R=0	0.09(±0.22)	0(±0)	1.59	
R=5	0.24(±0.52)	0(±0)	1.84	
R=15	0.42(±0.50)	0.04(±0.11)	5.21	*
R=30	0.70(±0.61)	0.07(±0.15)	9.03	*
R=45	0.89(±0.63)	0.52(±0.53)	2.01	
Dizziness				
R=0	0.39(±0.77)	0(±0)	2.32	
R=5	0.51(±0.77)	0(±0)	3.89	
R=15	0.89(±0.80)	0.04(±0.11)	10.15	*
R=30	1.18(±0.87)	0.11(±0.17)	13.00	*
R=45	1.35(±0.97)	0.22(±0.29)	11.15	*
Tingling				
R=0	0.24(±0.53)	0(±0)	1.67	
R=5	0.21(±0.46)	0(±0)	1.76	
R=15	0.24(±0.40)	0(±0)	2.91	
R=30	0.61(±0.99)	0(±0)	3.02	
R=45	0.79(±0.87)	0(±0)	6.68	*
Trembling				
R=0	0.09(±0.22)	0(±0)	1.59	
R=5	0.15(±0.41)	0(±0)	1.25	
R=15	0.18(±0.41)	0(±0)	1.8	
R=30	0.32(±0.44)	0.04(±0.11)	3.50	
R=45	0.52(±0.57)	0.04(±0.11)	6.19	*
Unreality				
R=0	0(±0)	0(±0)	.	
R=5	0(±0)	0(±0)	.	
R=15	0.18(±0.35)	0(±0)	2.47	
R=30	0.24(±0.40)	0(±0)	3.32	
R=45	0.42(±0.56)	0(±0)	5.12	*

Table 3-7. Continued

Palpitations	Female	Male	F	
R=0	0(±0)	0(±0)	.	
R=5	0(±0)	0(±0)	.	
R=15	0.05(±0.15)	0(±0)	0.81	
R=30	0.15(±0.23)	0(±0)	3.89	
R=45	0.30(±0.64)	0(±0)	2.00	
Fear of Losing Control				
R=0	0.27(±0.71)	0(±0)	1.31	
R=5	0.27(±0.55)	0.04(±0.11)	1.56	
R=15	0.35(±0.60)	0.04(±0.11)	2.35	
R=30	0.52(±0.81)	0.11(±0.17)	2.16	
R=45	0.94(±0.96)	0.26(±0.32)	4.07	*

Table 3-8. Male and Female change in (Delta) STAI Scores before and after the load presentation trial. The * indicated significant difference (p<0.05) for ME between breath number for a load magnitude.

Group	N	Median	25%	75%	Q	P<0.05
Female Delta State Anxiety	12	2.5	-1.5	9.5	6.6	
Male Delta State Anxiety	10	-0.5	-3	3	6.6	
Female Delta Trait Anxiety	12	3.5	-0.5	7	17.6	
Male Delta Trait Anxiety	10	-3	-4	-1	17.6	*

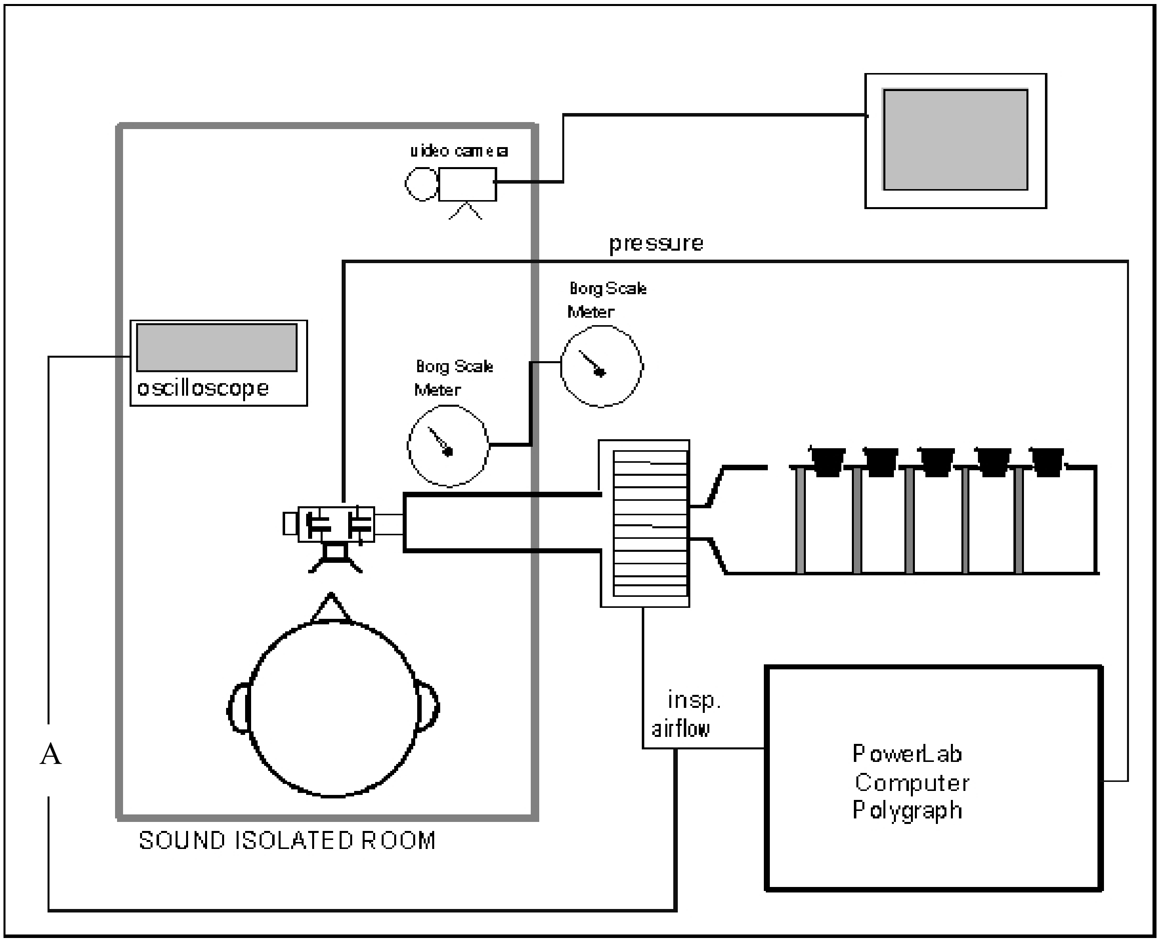
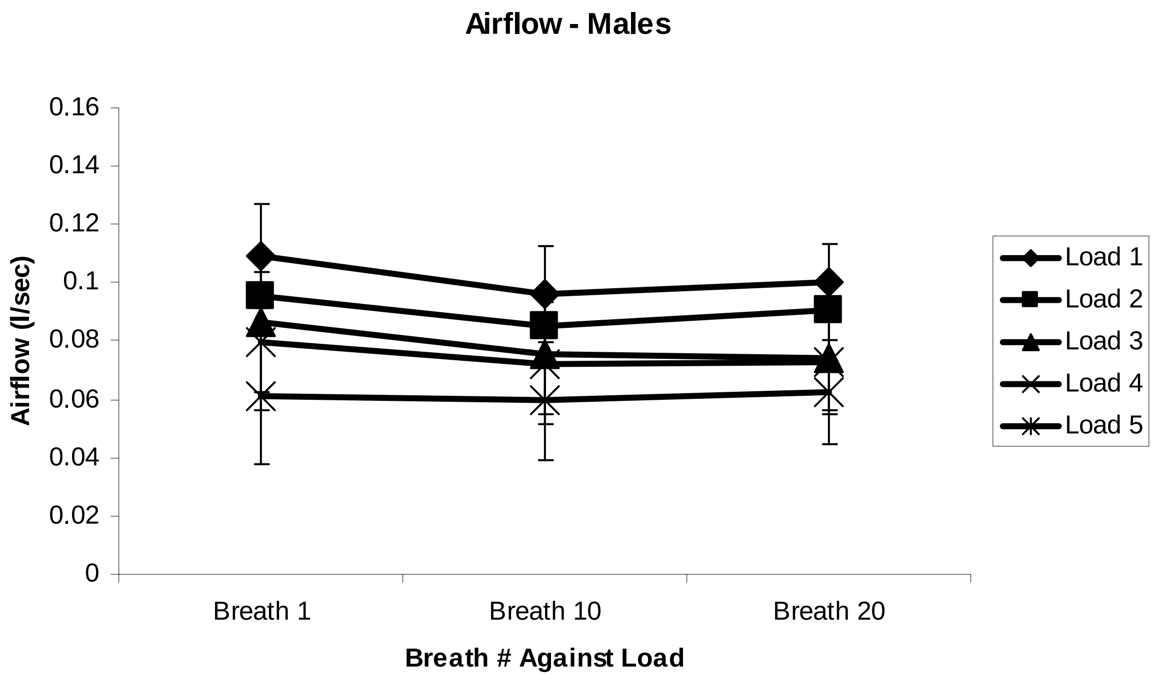
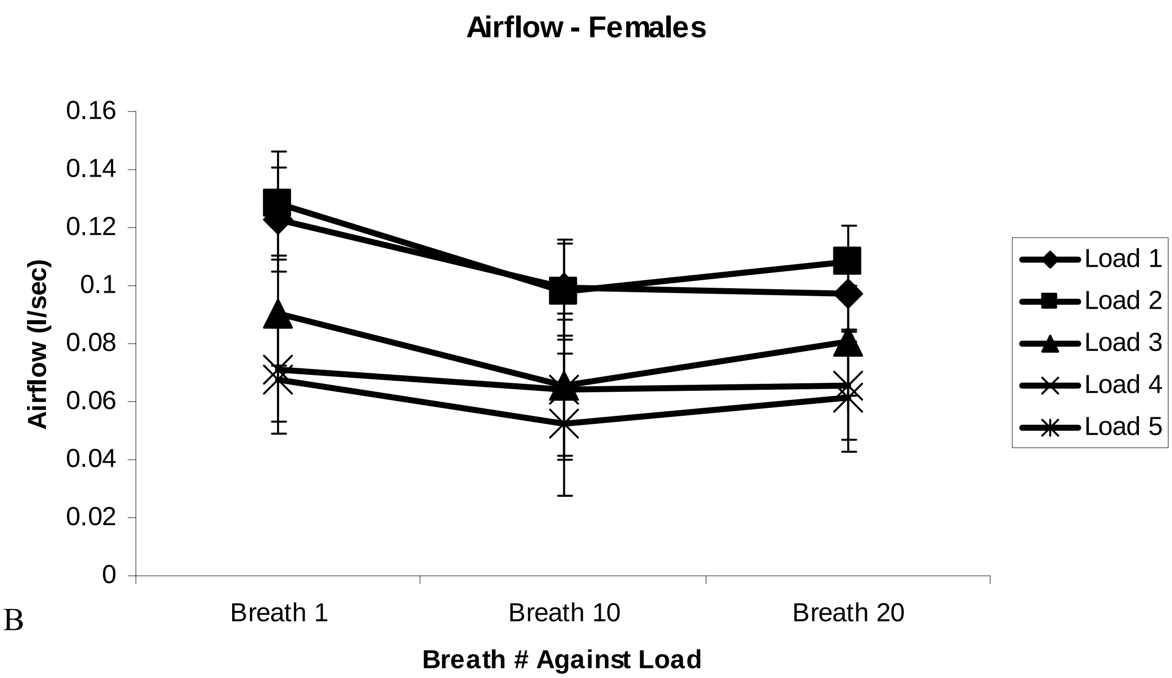


Figure 3-1 Experimental set up for experiment 2. Subjects were seated in a sound isolated room and separated from the experiment to avoid any detection and observation of experimental manipulations by the subject. Their image was observed via video camera but not recorded, and the resistive manifold was attached to the mouthpiece.

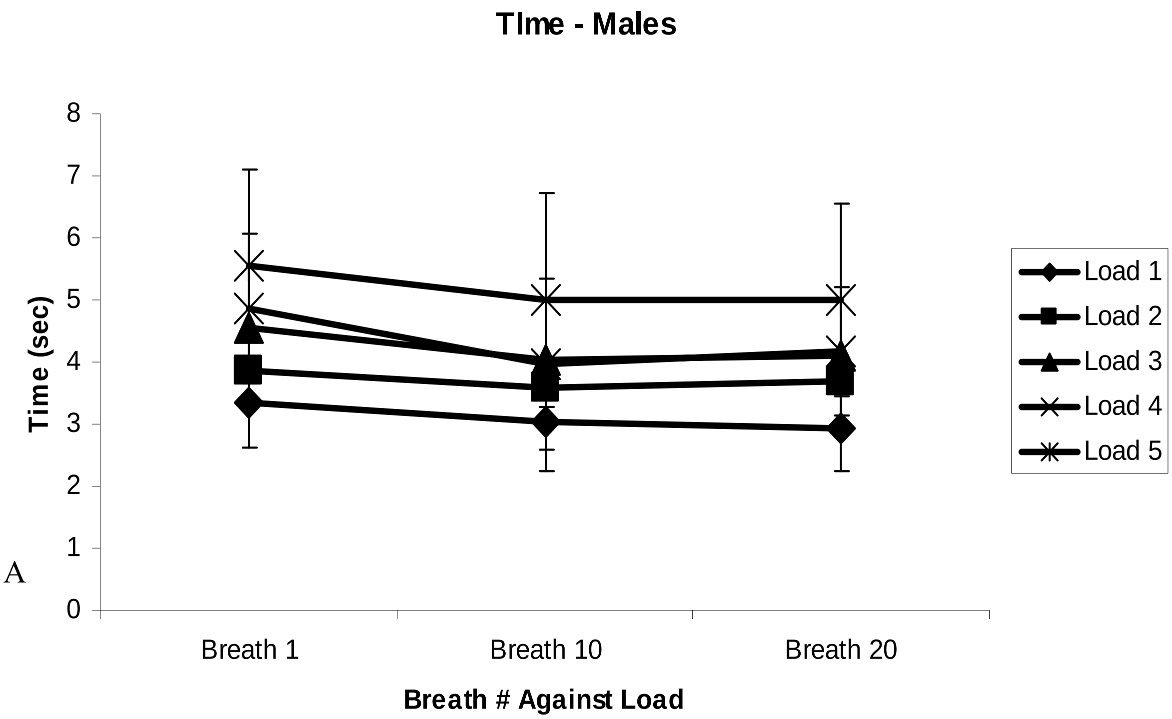


A

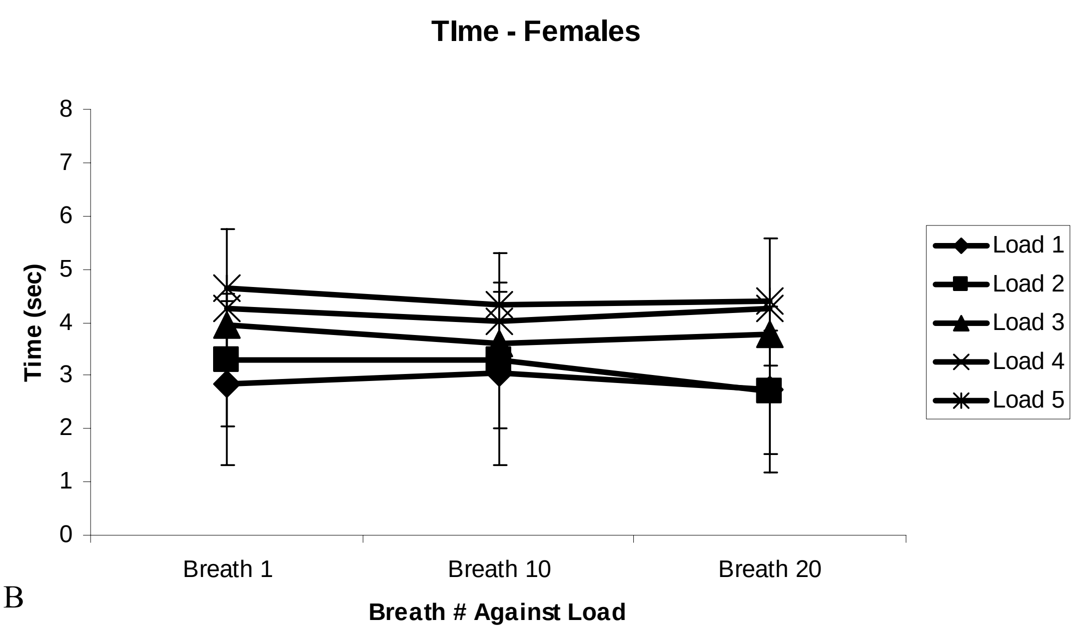


B

Figure 3-2. Mean (± standard deviation) airflow for A) males and B) females against each load magnitude.



A



B

Figure 3-3. Mean (± standard deviation) inspiratory time (Ti) for A) males and B) females against each load magnitude. There was no significant difference between the two groups.

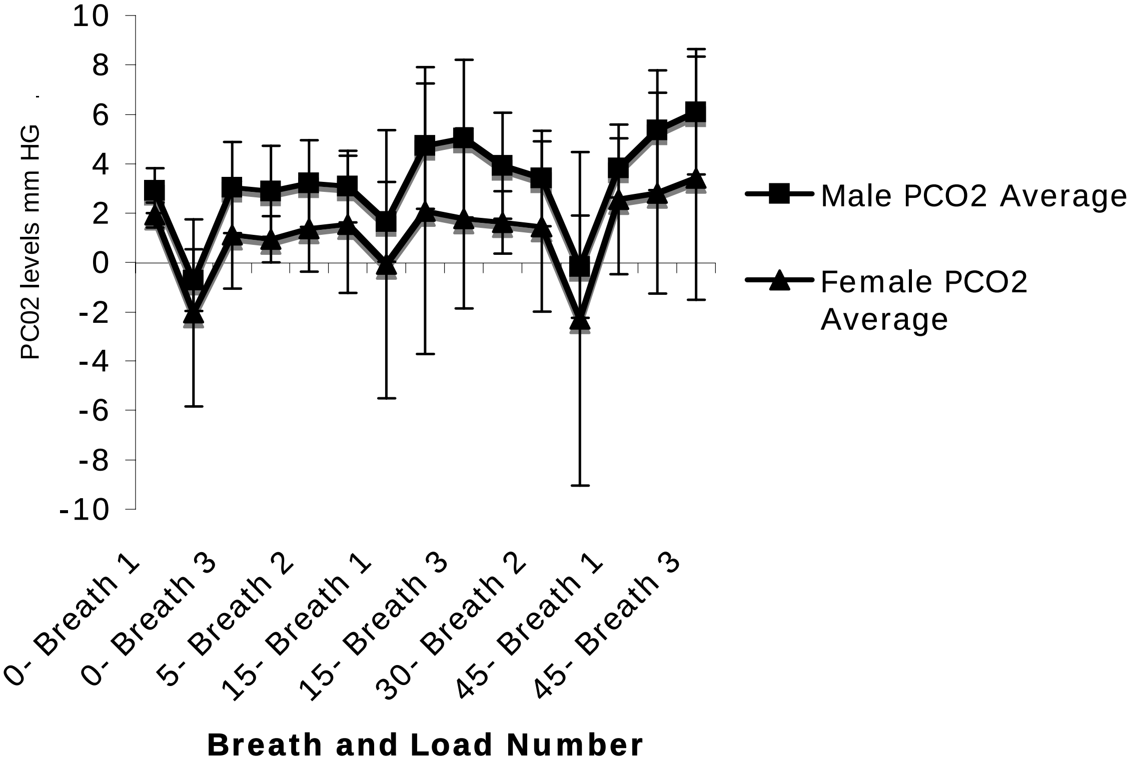
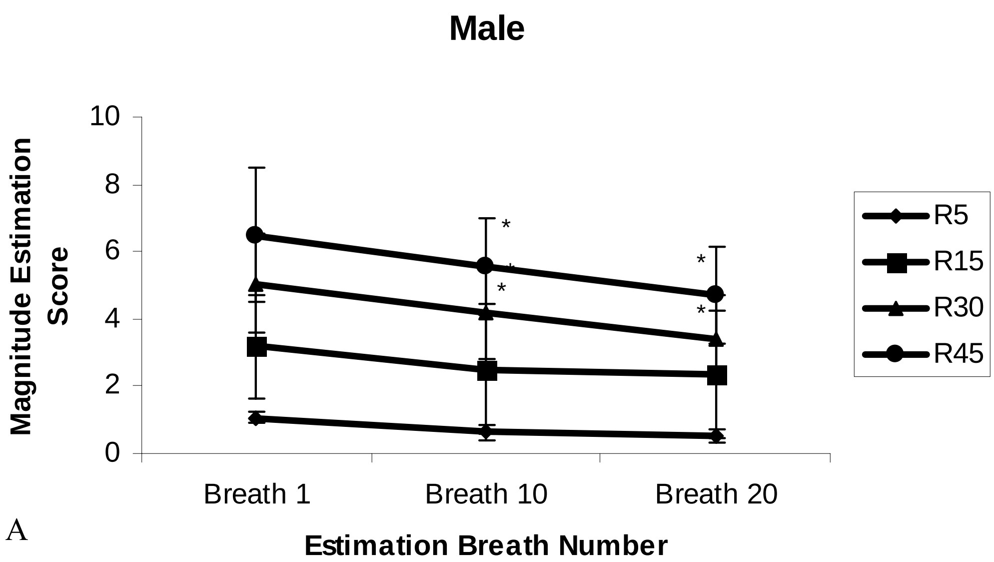
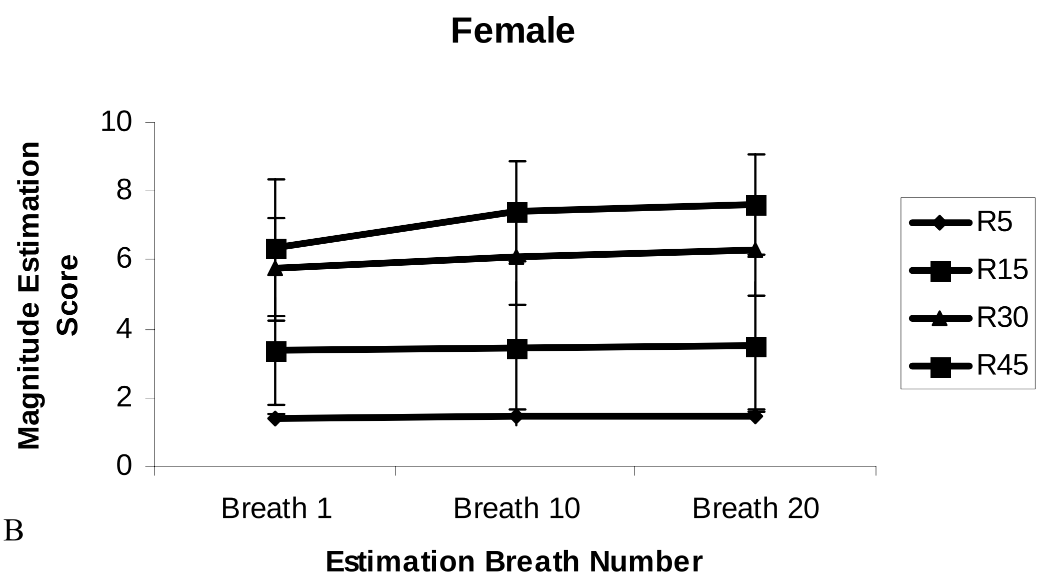


Figure 3-4. Mean (± standard deviation) PCO2 change for males and females against each load magnitude.



A



B

Figure 3-5. Mean (± standard deviation) magnitude estimation for A) males and B) females at breaths 1, 10 and 20 against each load magnitude.

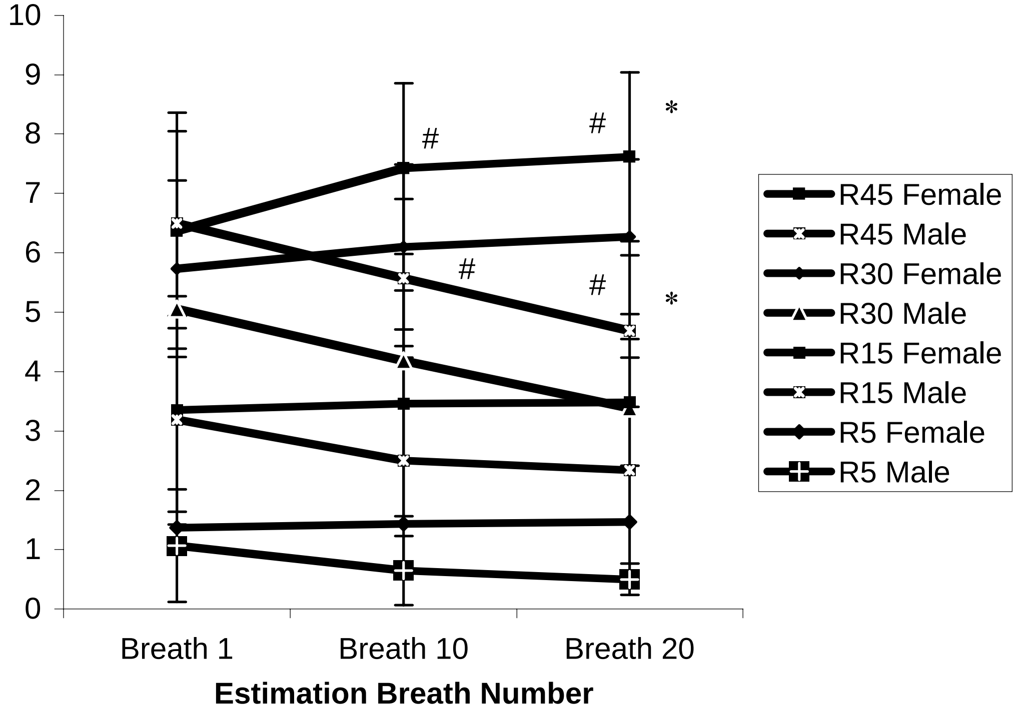
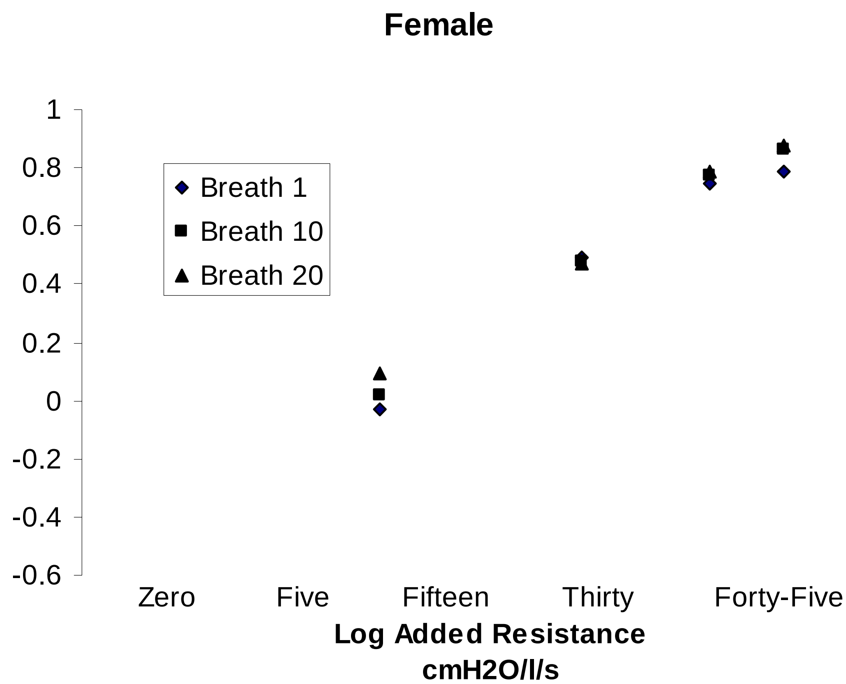
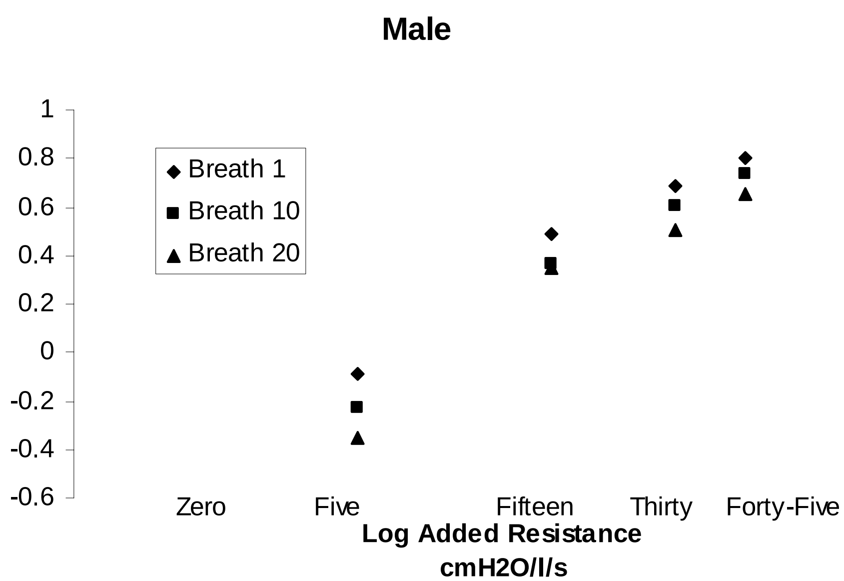


Figure 3-6. Mean (± standard deviation) magnitude estimation for both males and females at breaths 1, 10 and 20 against each load magnitude. The * indicated significant difference ($p<0.05$) for ME between breath number for a load magnitude. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and breath number.



A



B

Figure 3-7. Mean log of the magnitude estimation for A) females and B) males at breaths 1, 10 and 20 against each load magnitude.

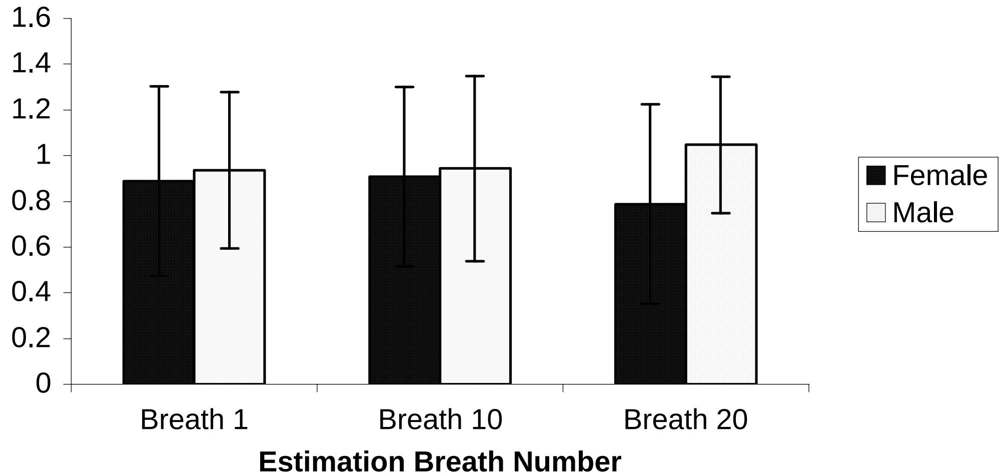


Figure 3-8. Mean (± standard deviation) log-log slope of the magnitude estimation-resistive load relationship for males and females at breaths 1, 10 and 20 against each load magnitude.

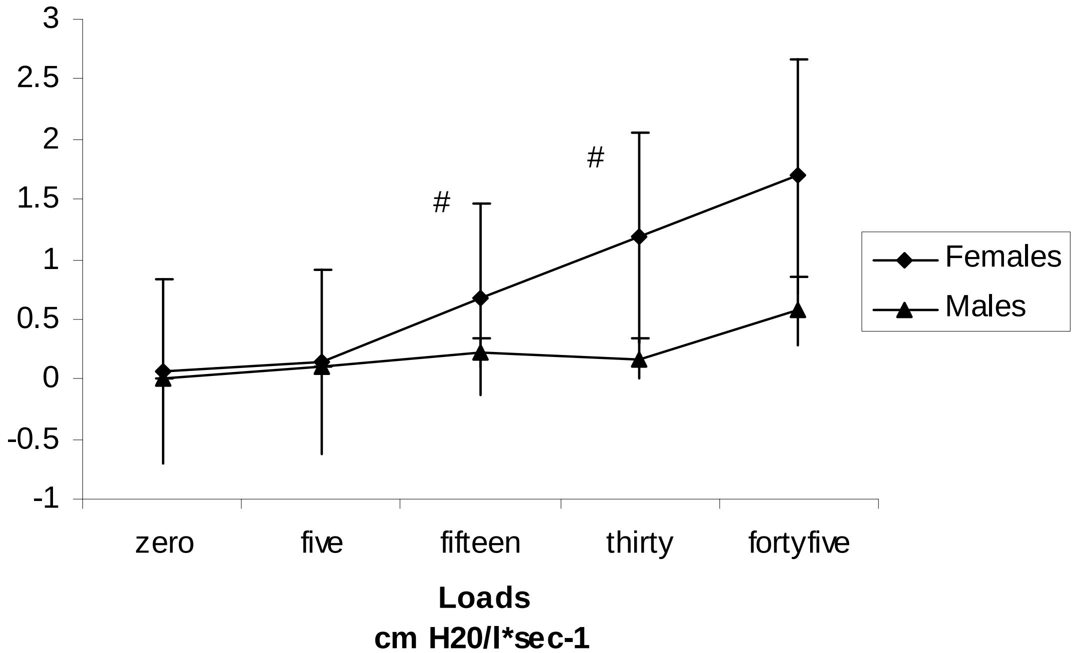


Figure 3-9. Mean (± standard deviation) subjective reporting of the general level of fear on a 0-10 scale in males and females. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and breath number.

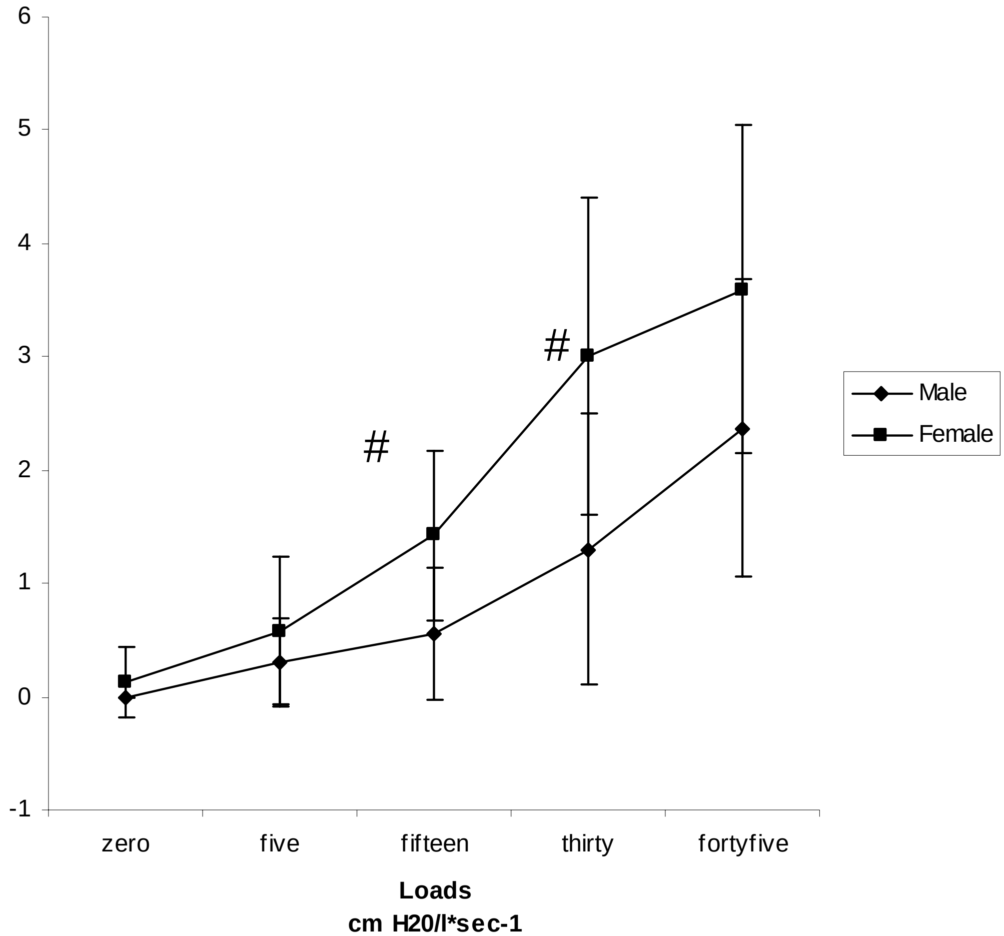


Figure 3-10. Mean (± standard deviation) subjective reporting of the general level of fear of suffocation on a 0-10 scale in males and females. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and breath number.

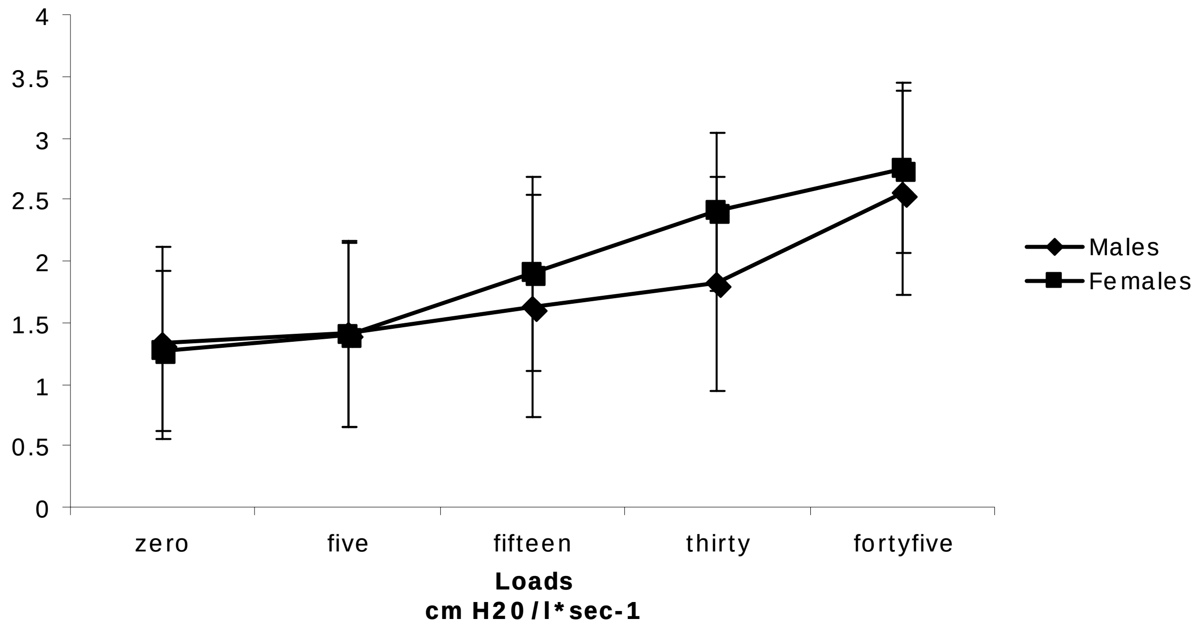


Figure 3-11. Mean (± standard deviation) subjective reporting of the level of distress according to the Self-Assessment Maniken (SAM) Rating Scale in males and females. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and breath number.

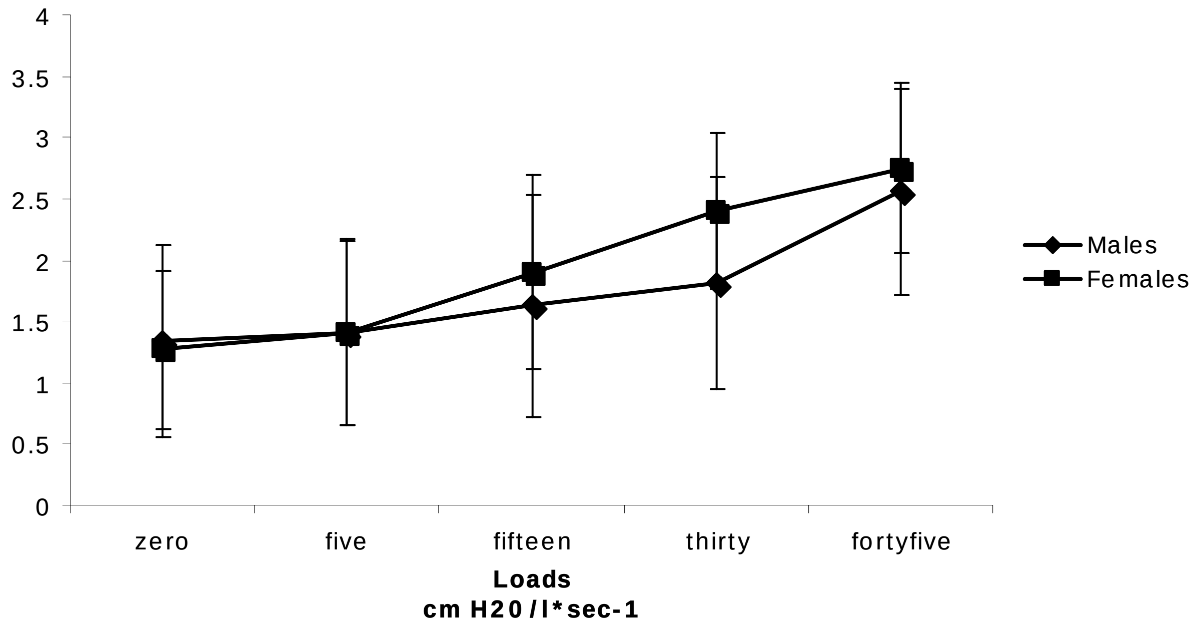


Figure 3-12. Mean (± standard deviation) subjective reporting of the level of control according to the Self-Assessment Maniken (SAM) Rating Scale in males and females. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and breath number. For this measurement, there was no significant difference between sexes.

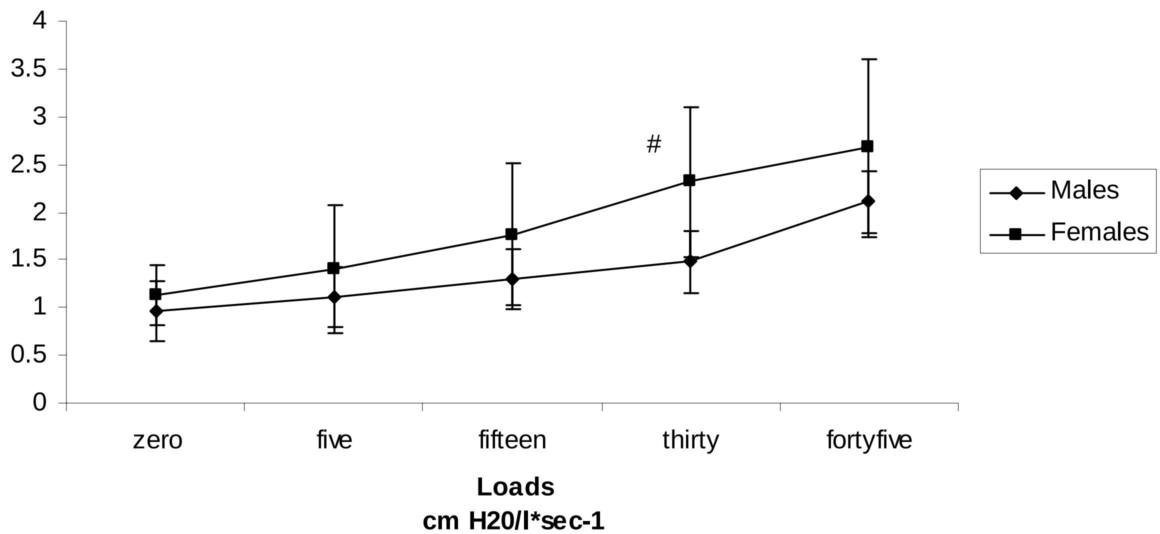


Figure 3-13. Mean (± standard deviation) subjective reporting of the level of chest pressure according to the Self-Assessment Maniken (SAM) Rating Scale in males and females. The # indicates a significant difference (p<0.05) between sexes for the corresponding load magnitude and breath number.

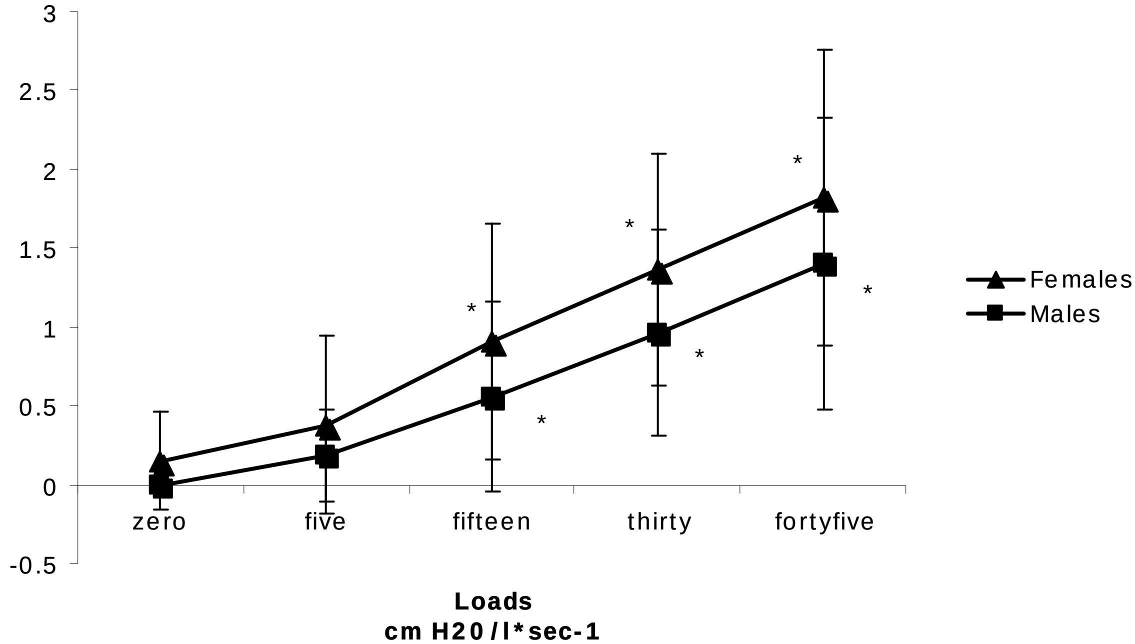


Figure 3-14. Mean (± standard deviation) subjective reporting of the level of dyspnea according to Diagnostic Symptoms Questionnaire (DSQ) Body Sensation Questionnaire in males and females. The * indicated significant difference ($p<0.05$) for rating for a load magnitude. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and rating.

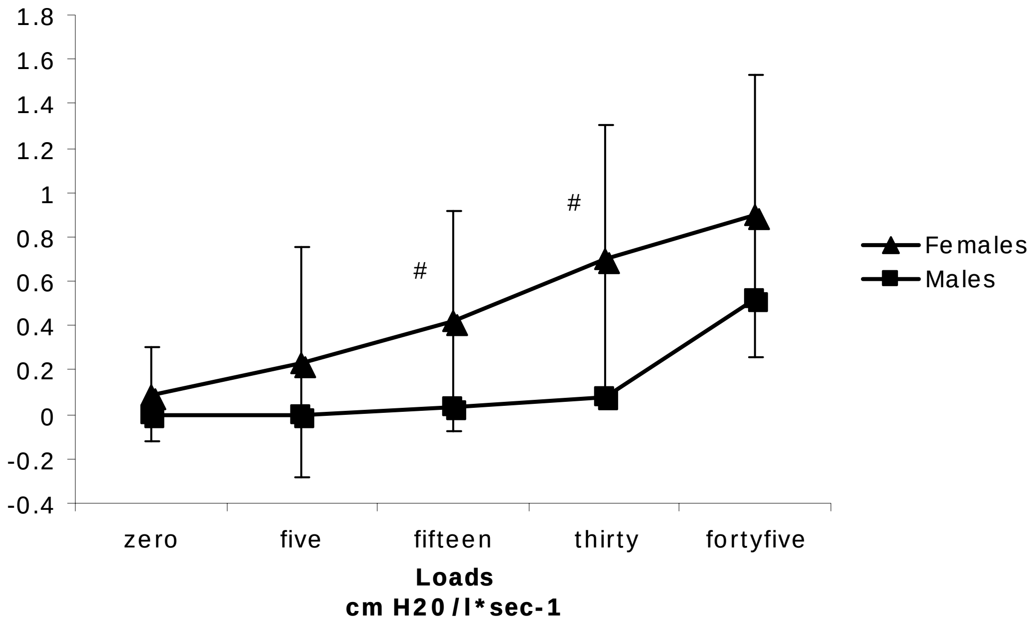


Figure 3-15. Mean (± standard deviation) subjective reporting of the level of faintness according to Diagnostic Symptoms Questionnaire (DSQ) Body Sensation Questionnaire in males and females. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and rating.

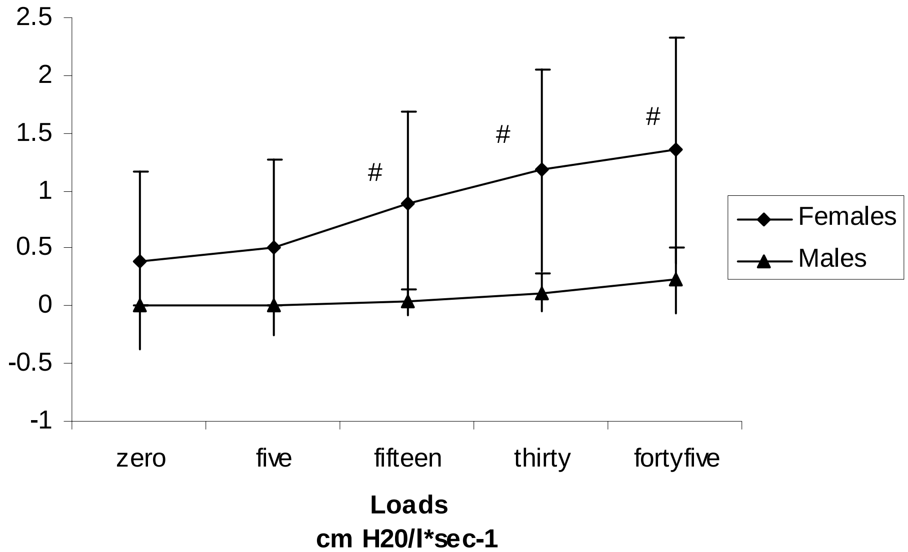


Figure 3-16. Mean (± standard deviation) subjective reporting of the level of dizziness according to Diagnostic Symptoms Questionnaire (DSQ) Body Sensation Questionnaire in males and females. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and rating.

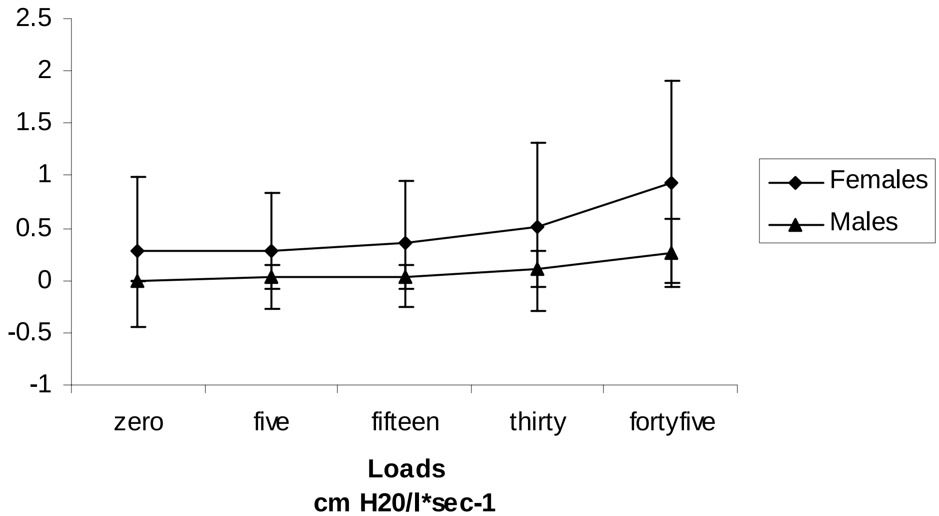


Figure 3-17. Mean (± standard deviation) subjective reporting of the fear of losing control according to Diagnostic Symptoms Questionnaire (DSQ) Body Sensation Questionnaire in males and females. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and rating.

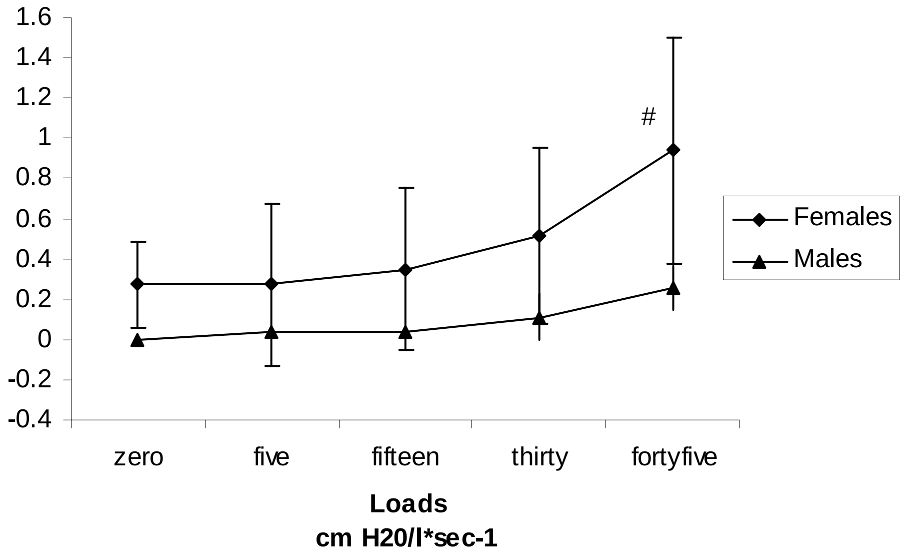


Figure 3-18. Mean (± standard deviation) subjective reporting of the level of trembling according to Diagnostic Symptoms Questionnaire (DSQ) Body Sensation Questionnaire in males and females. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and rating.

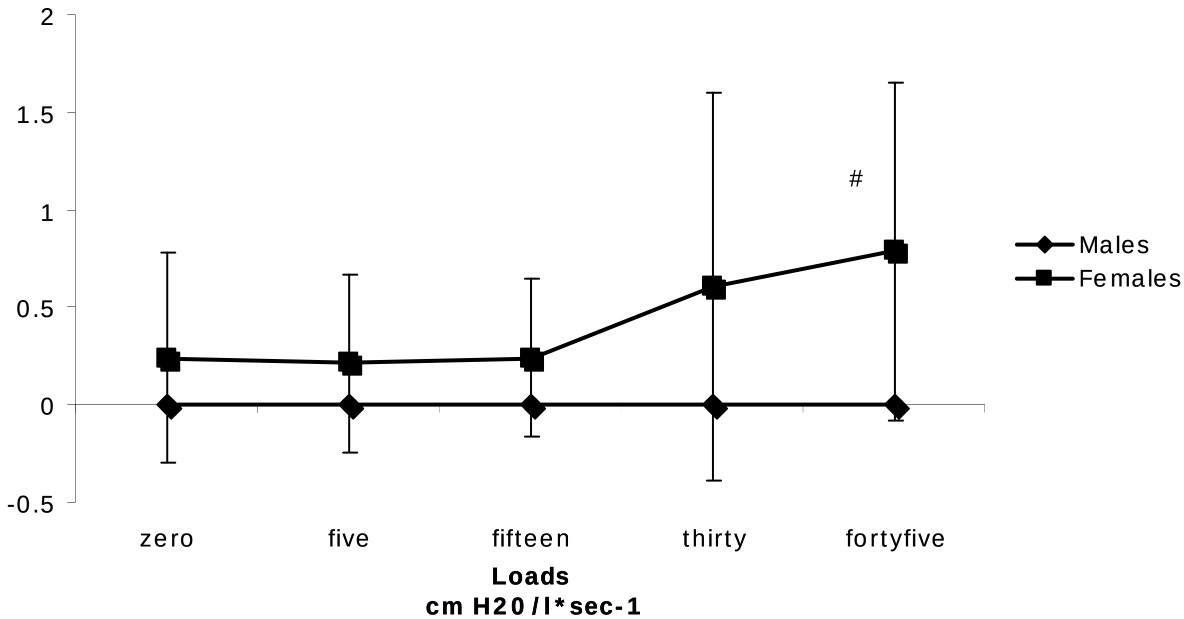


Figure 3-19. Mean (± standard deviation) subjective reporting of the level of tingling according to Diagnostic Symptoms Questionnaire (DSQ) Body Sensation Questionnaire in males and females. The # indicates a significant difference (p<0.05) between sexes for the corresponding load magnitude and rating.

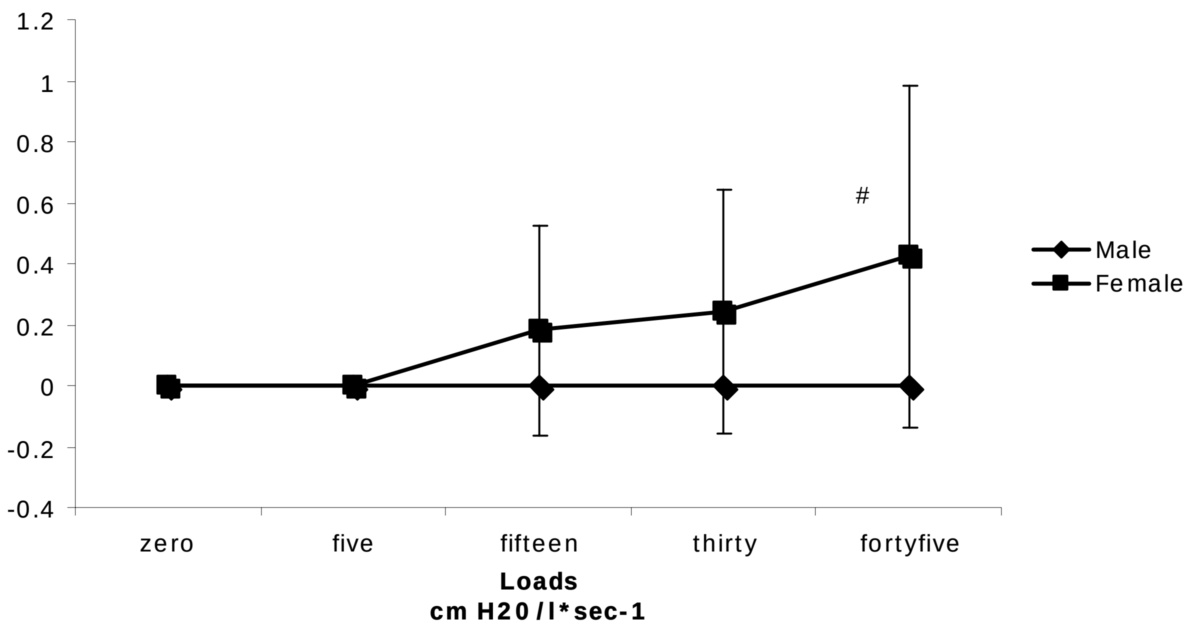


Figure 3-20. Mean (± standard deviation) subjective reporting of the level of sense of unreality according to Diagnostic Symptoms Questionnaire (DSQ) Body Sensation Questionnaire in males and females. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and rating.

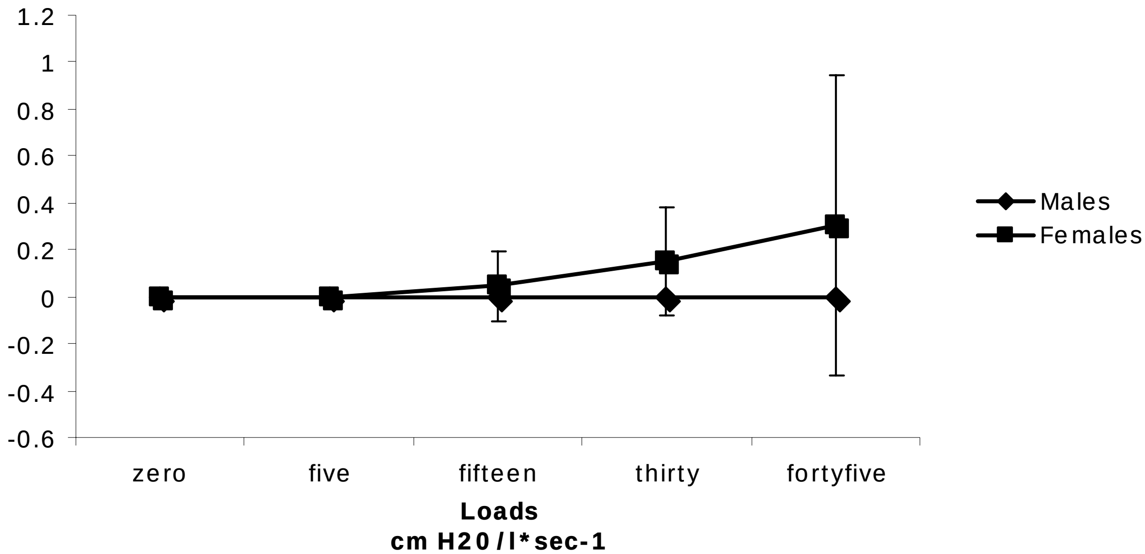


Figure 3-21. Mean (± standard deviation) subjective reporting of the level of palpitations according to Diagnostic Symptoms Questionnaire (DSQ) Body Sensation Questionnaire in males and females. The # indicates a significant difference ($p<0.05$) between sexes for the corresponding load magnitude and rating.

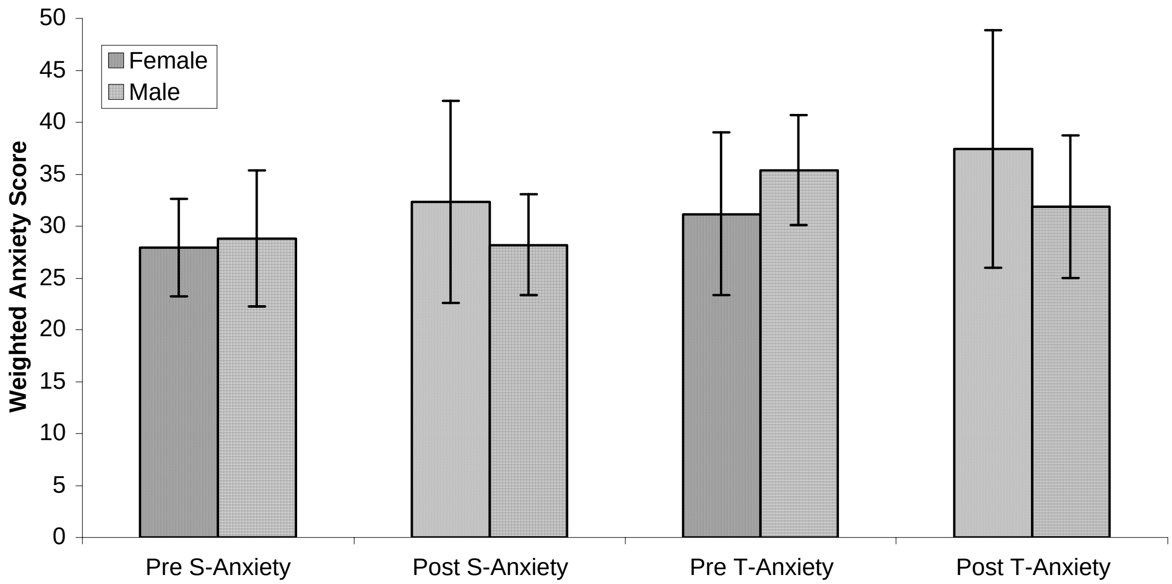


Figure 3-22. Mean (± standard deviation) STAI scores for state (S) anxiety and trait (T) anxiety. There were no significant difference pre- and post- load presentation trial and between sexes for state and trait anxiety scores.

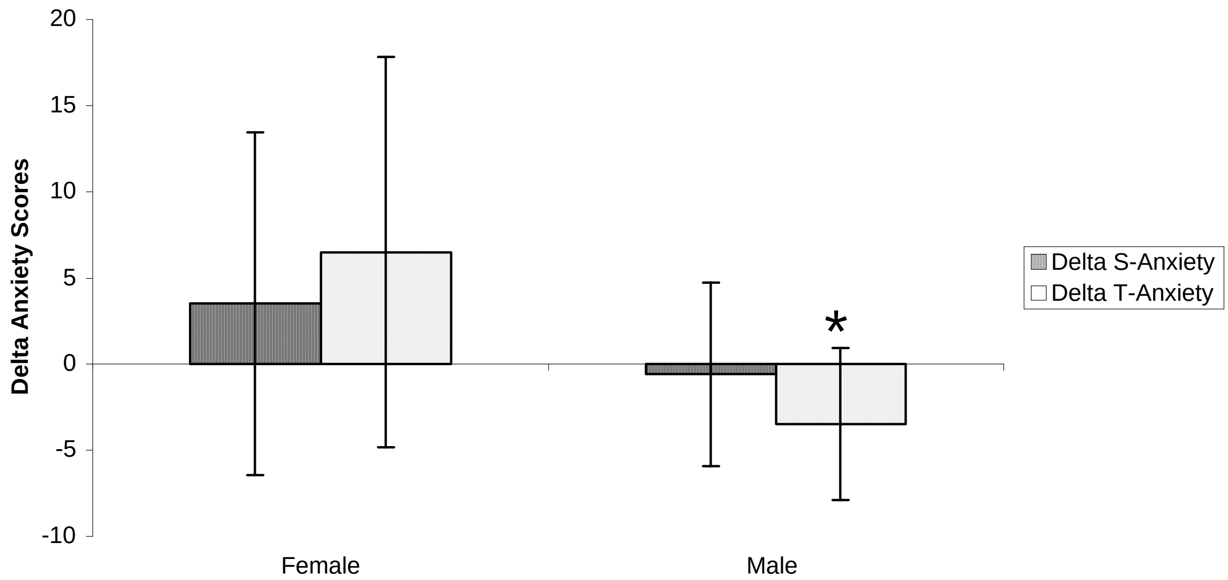


Figure 3-23. Mean (± standard deviation) change (Delta) in STAI scores for state (S) anxiety and trait (T) anxiety pre- and post-load presentation trial. There was no significant difference for female Delta S-anxiety and Delta T-anxiety pre- and post-load presentation. Males had a significant decrease in Delta T-anxiety pre- and post-load presentation but no significant different for Delta S-anxiety.

CHAPTER 4
PERCEPTION AND SUBJECTIVE RATINGS OF SUSTAINED BREATH RESISTIVE LOADS IN MALES AND FEMALES FINAL DISCUSSION

Emotions can be discriminated most successfully by the respiratory component (Nyklicek et. al., 1997). Central neural correlates of anxiety, such as the amygdala and insulate cortex, are activated during respiratory distress (Masaoka and Homma, 2000). Likewise, it is reasonable to deduce that respiratory distress elicits an affective response similar to anxiety. However, no study has been done to determine the relationship between emotional responses and respiratory resistive loads. This is the first study to combine ventilatory pattern, magnitude estimation, and subjective measures with inspiratory loading. The results of this study demonstrate for all subjects, an increase in somatosensory and behavioral measures of stress and aversive responses as a function of increasing load and increasing duration of breathing against the loads. The results further demonstrate that males and females respond differently to sustained breathing against inspiratory resistive loads particularly within the realm of the affective dimension of respiratory somatosensation.

Davenport and Kifle (2001) reported that children with life-threatening asthma (LTA) have unique decreased perceptual sensitivity and processing deficit to inspiratory loads. While LTA patients include males and females, the asthmatic children that had reduced perception sensitivities and increased detection thresholds were males (Davenport and Kifle, 2001). This cannot be explained by differences in respiratory effort, airway mechanics, or task performance ability, but was reported to be due to central neural deficits evidenced by the absence of the respiratory-related evoked potential in LTA children with perceptual deficits (Kifle, Seng & Davenport, 1997; Kikuchi et al., 1994; Webster and Colrain, 2000). However, these studies only investigated the perception of single-breath resistive loads, which are a poor clinical correlate for the perception of mechanical respiratory disorders such as asthma and other forms of COPD.

This study differentiates between single breath somatosensation and affective sensations related sustained breathing against respiratory loads. The present study demonstrated a threshold for eliciting affective modulation of load perception (15 $cmH_2O/l*sec^{-1}$). For loads above this threshold, there was a relationship between the load magnitude, perceptual symptom reporting and number of breaths against the load. These results suggest that as the subjects increased their respiratory drive to compensate for the increased respiratory work of breathing, perceptual symptoms changed. Of particular interest, was the significant sex effect in the respiratory load modulation of perception. Whereas females tend to potentiate their processing and perception of the sustained loads, males exhibited symptom suppression in response to sustained breathing the load.

Males have higher mortality rates due to COPD than females (Thom 1989; Vollmer et al., 1992). The male symptom suppression results of the present study suggest morbidity from respiratory disorders may be due to symptom suppression. Males are less likely to seek medical care for respiratory disorders which may be due to an intrinsic tendency to decrease symptom perception and reduce the negative affect elicited from their illness. Dyspnea is perceived as less important for males on their quality of life scales than females (Jones 1992). As a result, decreased male patient initiation for medical care makes them at a higher risk for unnecessary exacerbation of their disease and ultimately, at higher risk for death. One of the primary causes of death from asthma is a delay in treatment of an asthmatic attack. The male symptom suppression of an asthma exacerbation dependent increased load to breathing may predispose males to greater risk of morbidity from asthma due delays in recognition of an asthma attack severity.

Alternatively, females will be more likely to seek medical care for discomfort and illness caused by respiratory distress. Contrary to the increase in male morbidity due to COPD, females report higher shortness of breath (Dales 1989; Krzyzanowski 1992; Krzyzanowski 1986; Guslvik 1979). Aversive respiratory stimuli may increase introspection, apprehension, negativity and perceptual focus on the body, which in turn lowers the perceptual threshold for somatic sensations (Van de Bergh 1995). As the present sustained-breath perceptual study demonstrates, females are not only more negatively affected by respiratory distress, they have a lower perceptual symptom threshold than men hence are more likely to quantify the extent of their increased respiratory load and respond more quickly.

Although females will be more likely to seek treatment for respiratory disorders, they will also be more negatively affected by them. Women with respiratory disorders such as COPD self-report more psychological distress than men (Lauren et al., 2007). Females are also more exposed to the psychological impairment that correlates with the dyspneic component of chronic obstructive pulmonary disease (Di Marco et. al., 2006). In the prolonged respiratory loading of the present experiment, there was a significant increase in female subjective responses such as fear, trembling, tingling, faintness, and fear of losing control. Women affected by pulmonary disease report less confidence in their ability to control their respiratory symptoms and have reduced quality of life than men dealing with the same disease (Laurin et al., 2007).

This increase in negative affectivity as well as exacerbation of the perception of the loads can result in a long-term state of anxiety or depression. Psychiatric disorders are three times more common in COPD patients, and are two times higher in females than in males (Laurin et. al., 2007). Psychological factors such as depression have been linked to the reporting of respiratory symptoms, though sex differences in rates of reporting by psychological status have not been determined (Becklake and Knauffman, 1999). Hence, the results of this study support the hypothesis that obstructed breathing is aversive for all individuals and females should be more prone to respiratory elicited anxiety.

Males also differ from females in their effect of sustained breathing against inspiratory loads in the change in emotional state (state-trait anxiety). Patient's emotional reaction to a sense of breathlessness exacerbates their perception of breathlessness (Bailey et al., 1994), and females demonstrated a more emotional reaction to prolonged inspiratory loading, i.e females had a tendency to increase state and trait anxiety whereas males tended to decrease pre- and post loaded breathing. Although these states may be transitory, they can recur when evoked by recurrent or inescapable appropriate stimuli from pulmonary disease and may endure over time particularly if the evoking stimuli condition the subject to the aversive resistive load. The significantly increased incidence of anxiety disorders and lower quality of life in females experiencing respiratory diseases supports this most behavioral load conditioning effect. This can result in excessive medication intake, unwarranted illness behavior and hospitalization that is often seen in the "overperceiver" group of patients who report symptoms in excess of the physiological abnormality they are presented (Put et. al, 1999; Put et. al., 2000).

Thus, breathing and anxiety responses can be mediated by both conscious and subconscious processes. These responses differ between sexes and result in a varying perception and response to breathing disturbances. Awareness of these significant sex differences will allow clinicians to educate male patients to be subjectively aware of their respiratory disorders. Likewise, female patients should be managed using preventative care immediately upon diagnosis of chronic obstructive pulmonary disease to avoid onset of depression or other anxiety disorders.

APPENDIX A
DIAGNOSTIC SYMPTOM QUESTIONNAIRE

To which extent have you experienced the following symptoms during the previous application stimulus? Please circle the correct answer.

1. Tingling sensations:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

2. Fear of losing control:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

3. Faintness:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

4. Dyspnea:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

5. Fear of dying:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

6. Unreality:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

7. Hot/cold flushes:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

8. Trembling:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

9. Choking:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

10. Fear of going crazy:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

11. Abdominal Distress:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

12. Chest pain:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

13. Palpitations:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

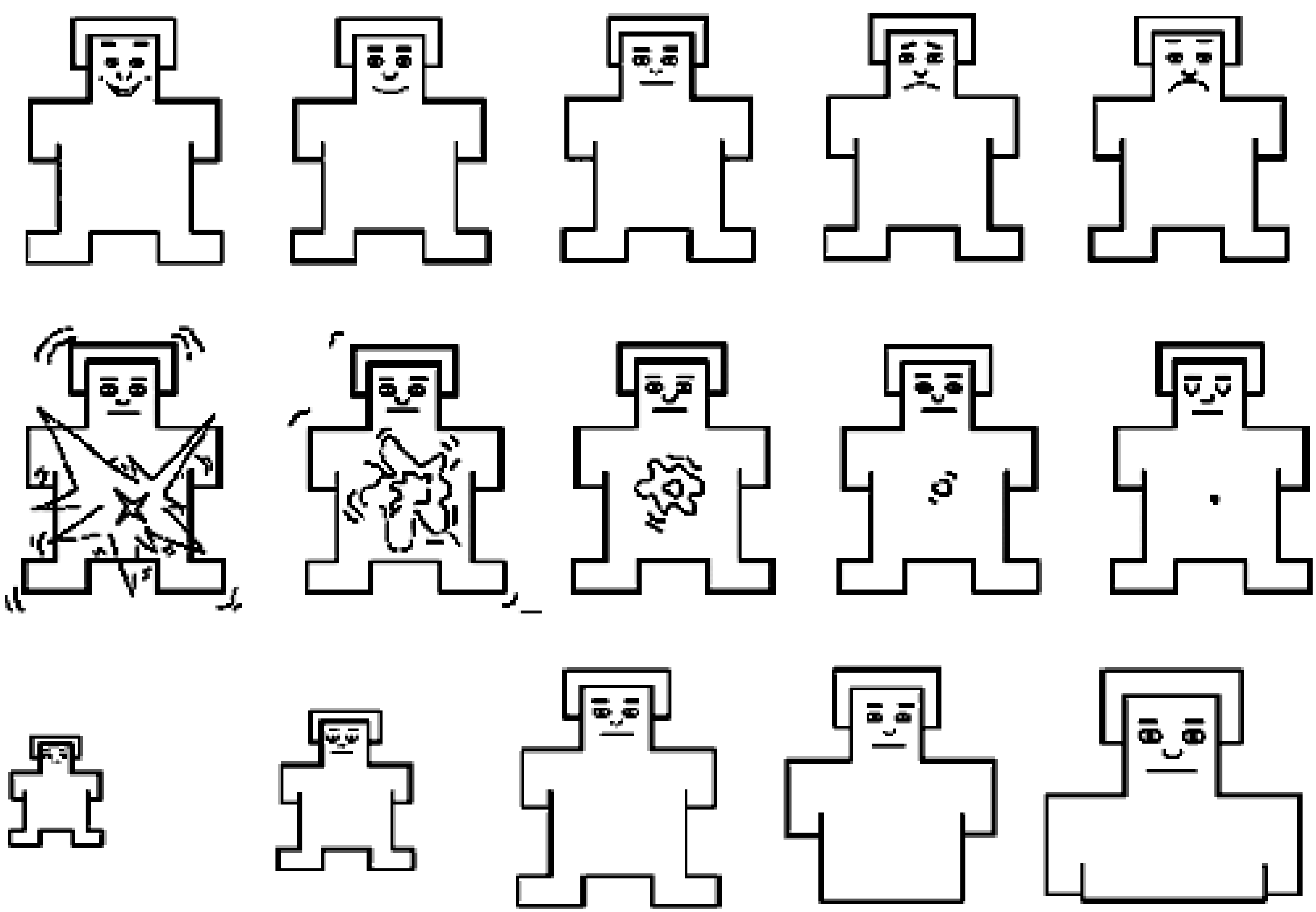
14. Sweating:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

15. Dizziness:

0	1	2	3	4
not at all	slight	moderate	severe	very severe

APPENDIX B
SUBJECTIVE ASSESSMENT MANIKEN RATING HAPPINESS, CHEST PRESSURE, AND CONTROL



APPENDIX C

Please circle the level of **fear** you have experienced during the previous application of the bodily stimulus	Please circle the level of **fear of suffocation** you have experienced during the previous application of the bodily stimulus
0 Nothing at all	**0** Nothing at all
1 Very slight	**1** Very slight
2 Slight	**2** Slight
3 Moderate	**3** Moderate
4 Somewhat severe	**4** Somewhat severe
5 Severe (heavy)	**5** Severe (heavy)
6	**6**
7 Very severe	**7** Very severe
8	**8**
9	**9**
10 Very, very severe (almost maximal)	**10** Very, very severe (almost maximal)

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