RESPIRATORY MECHANICS DURING UPPER-BODY EXERCISE IN HEALTHY HUMANS

A thesis submitted for the degree of Doctor of Philosophy

by

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ABSTRACT

The physiological responses to upper-body exercise (UBE) are well established. Few published studies, however, have attempted to elucidate the mechanical ventilatory responses to UBE. There is empirical evidence that respiratory function may be compromised by UBE during which the ventilatory and postural functions of the 'respiratory' muscles may be exacerbated. Therefore, the aims of this thesis were: 1) to characterise the mechanical-ventilatory responses to UBE in healthy subjects; 2) to explore the putative mechanisms that underpin the respiratory responses to UBE; and 3) to assess whether the mechanical-ventilatory stress imposed by UBE induces contractile fatigue of the respiratory muscles. Compared to lower-body exercise (LBE; leg cycling) at ventilation-matched work rates, UBE (arm-cranking) resulted in constraint of tidal volume, higher respiratory frequency, and greater neural drive to the respiratory muscles. Furthermore, end-expiratory lung volume was significantly elevated during peak UBE compared to LBE (39 ± 8 vs. 29 ± 8% vital capacity, $p < 0.05$) and was independent of expiratory flow limitation. In assessing the influence of cadence on cardiorespiratory function and respiratory mechanics, submaximal arm-cranking at high cadence (90 rev·min^{-1}) induced significantly greater cardiorespiratory stress, a trend towards elevated intra-thoracic pressures and significantly greater perceptions of dyspnoea than at low cadence (50 rev·min^{-1}). Furthermore, there was a greater prevalence of locomotor-respiratory coupling at high cadences ($p < 0.05$), suggestive of greater antagonistic loading of the thoracic muscles, likely the result of static postural contractions. Finally, there was objective evidence of abdominal muscle contractile fatigue in response to severe- but not heavy-intensity UBE. Specifically, there was a 22% decrease in gastric twitch pressure from pre- to post-exercise in response to magnetic stimulation of the thoracic nerves ($p < 0.05$). However, there was limited evidence of exercise-induced diaphragm fatigue, as assessed using magnetic stimulation of the phrenic nerves ($p > 0.05$). In conclusion, mechanical-ventilatory function may be compromised during UBE due to complex interactions between thoracic muscle recruitment, central neural drive and thoracic volume displacement. This thesis presents novel findings which may have important functional implications for clinical populations who report breathlessness during activities of daily living that involve the upper-body, as well as for athletes engaged in upper-body sports.

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"*Pluralitas non est ponenda sine neccesitate"* – Occam’s Razor

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SYMBOLS AND ABBREVIATIONS

BTPS	Body temperature and pressure saturated
$[Ca^{2+}]$	Calcium ion concentration
CMAP	Compound muscle action potential
CMS	Cervical magnetic stimulation
CO_2	Carbon dioxide
CT	Contraction time
CV	Coefficient of variation
EC	Excitation-contraction
EELV	End-expiratory lung volume
EILV	End-inspiratory lung volume
EMG	Electromyogram
EMG_{RMS}	Root-mean squared of EMG signal
f_C	Cardiac frequency
FEV_1	Forced expiratory volume in 1 second
f_R	Respiratory frequency
FRC	Functional residual capacity
FVC	Forced Vital Capacity
HFF	High-frequency fatigue
IC	Inspiratory capacity
ICC	Interclass correlation
[BLa]	Blood lactate concentration
LFF	Low-frequency fatigue
LRC	Locomotor-respiratory coupling
MRR	Maximal rate of relaxation
MVC	Maximal voluntary contraction
MVV	Maximal voluntary ventilation
$[Na^{2+}]$	Sodium ion concentration
O_2	Oxygen
Pdi	Transdiaphragmatic pressure
$P_{di,tw}$	Twitch transdiaphragmatic pressure
P_{Emax}	Maximal expiratory pressure
P_ECO_2	Partial pressure of mixed expired carbon dioxide
Pga	Gastric pressure

$\mathbf{P_{ga,tw}}$	Twitch gastric pressure
$\mathbf{P_{Imax}}$	Maximal inspiratory pressure
Poe	Oesophageal pressure
$\mathbf{P_{oe,tw}}$	Twitch oesophageal pressure
RA	Rectus abdominis
RPE	Rating of perceived exertion
$\mathbf{RT_{0.5}}$	Half-relaxation time
RV	Residual volume
SD	Standard deviation
$\mathbf{SpO_2}$	Arterial oxygen saturation
$\mathbf{T_E}$	Expiratory time
$\mathbf{T_I}$	Inspiratory time
TLC	Total lung capacity
$\mathbf{T_{LIM}}$	Time to the limit of tolerance
$\mathbf{T_{TOT}}$	Total respiratory time
$\mathbf{T_I/T_{TOT}}$	Inspiratory duty cycle
$\mathbf{T_E/T_{TOT}}$	Expiratory duty cycle
$\mathbf{\dot{V}CO_2}$	Minute carbon dioxide production
$\mathbf{\dot{V}_E}$	Minute ventilation
$\mathbf{\dot{V}O_2}$	Minute oxygen uptake
$\mathbf{\dot{V}O_{2max}}$	Maximal minute oxygen uptake
$\mathbf{\dot{V}O_{2FC}}$	Minute oxygen uptake fast component
$\mathbf{\dot{V}O_{2peak}}$	Peak minute oxygen uptake
$\mathbf{\dot{V}O_{2SC}}$	Minute oxygen uptake slow component
$\mathbf{\dot{V}O_{2TC}}$	Minute oxygen uptake time constant
$\mathbf{V_T}$	Tidal volume
$\mathbf{V_T/T_I}$	Mean inspiratory flowrate
$\mathbf{W_b}$	Work of breathing
$\mathbf{W_{max}}$	Maximal work rate
$\mathbf{W_{peak}}$	Peak work rate

Chapter One

GENERAL INTRODUCTION

Different modes of exercise result in distinct physiological outcomes. This notion is neither original nor contemporary. The physiological differences between upper-body exercise (UBE) and lower-body exercise (LBE) were characterised as early as the 1920s when Collett and Liljestrand, (1924) first reported that arm-cranking elicited greater physiological strain, at a given metabolic rate, than either leg-cycling or stair climbing. Until the 1960s, however, there were less than a dozen published papers on the physiological responses to dynamic UBE. It has since been recognised that the upper-extremities have a wide variety of applications in industry (Ford & Hellerstein, 1958; Ford, Hellerstein & Turell, 1959), agriculture (Nag, 1984), space exploration (Gazenko *et al*., 1980) in addition to a distinct role in able-bodied and disabled sports performance. As a result, research into UBE has gained momentum and several authors have replicated the early studies of Collett and Liljestrand (e.g. Asmussen and Hemmingsen, 1958; Astrand and Saltin, 1961; Bergh, Kanstrup & Ekblom, 1976; Sawka, Miles, Petrofsky, Wilde & Glaser, 1982; Martin, Zeballos & Weisman, 1991; Schneider, Wing & Morris, 2002). Such research has been succeeded by numerous authors in the contemporary literature to be discussed.

Despite nearly a century of research on the physiological responses to UBE, there is still limited data pertaining to breathing mechanics and respiratory muscle function during this exercise modality. This is due, in part, to the sophisticated techniques required to adequately quantify these phenomena. Indeed, a deeper understanding of the respiratory responses to whole-body exercise has only been possible since the widespread application of electromyography in the assessment of respiratory muscle activation (Lopata, Evanich & Lourenco, 1977; Lahrmann *et al.*, 1999; Luo & Moxham, 2005), oesophageal balloon-catheters in the assessment of intra-thoracic pressures (Mead, Mcilroy, Selverstone, & Kriete, 1955; Milic-Emili, 1984) and electromagnetic stimulation in the assessment of respiratory muscle fatigue (Aubier, Farkas, De Troyer, Mozes & Roussos, 1981; Johnson, Babcock, Suman, & Dempsey, 1993; Taylor *et al.,* 2006). Few studies, however, have applied these techniques in the context of UBE.

High-intensity, whole-body exercise, i.e. that requiring a 10 to 15 fold increase in minute ventilation, encroaches on the capacity of the respiratory system to generate volume and flow (Johnson, Aaron, Babcock, & Dempsey, 1996). By contrast, maximal UBE performed by healthy, able-bodied participants is not considered sufficient to induce maximal cardiorespiratory stress due to the smaller volume of active muscle mass and lower oxidative capacity (Seals and Mullin, 1982; Sawka *et al.*, 1982; Martin *et al.*, 1991; Alison *et al.*, 1998). There may be, however, alternative mechanisms by which UBE may impact negatively on respiratory efficiency. Since many of the respiratory muscles also contribute to power generation during UBE, Sawka, (1986)

postulated that there may be a subsequent impact on breathing patterns, respiratory muscle activation and respiratory muscle fatigue. There is empirical evidence to support this hypothesis. Several muscles of the thorax, including the superficial abdominals, diaphragm and erector spinae, have been shown to contract phasically prior to, or during, repetitive arm movements (Hodges and Gandevia, 2000; Zedka and Prochazka, 1997). Furthermore, unsupported arm exercise may affect respiratory muscle recruitment and increase intra-thoracic pressures in a manner that is independent of metabolic demand or ventilatory drive (Celli, Criner & Rassulo, 1985; Couser, Martinez & Celli, 1992). As a result, UBE may be capable of compromising respiratory efficiency by disrupting the causal relationship between neural drive to the respiratory muscles and the resultant volume displacement of the lung. A paucity of studies on healthy respiratory mechanics during UBE, however, means there is currently no consensus on the typical response and potential repercussions.

This thesis, therefore, focuses on the healthy respiratory responses to UBE. Further investigations in this area may have broad implications. For example, individuals with COPD report an increased intensity of dyspnoea and exercise intolerance during activities requiring heavy use of the upper-limbs (Porto *et al.,* 2009; Colucci *et al.,* 2010). This may, in turn, negatively impact on pulmonary rehabilitation programmes and activities of daily living. A greater mechanistic understanding of the loads imposed on the thoracic muscles during UBE, in addition to the influence of UBE on neural respiratory drive, may help inform clinical practice. Data from this thesis may also inform athletic training programmes for those engaged in upper-body dependent sports, e.g. kayaking, rowing, swimming and disability sport. Furthermore, data regarding the 'typical' respiratory outcomes of UBE may make it easier to identify instances of disordered breathing in otherwise healthy individuals.

A thorough discussion of the available literature relevant to this thesis follows in the next section. Based on the aforementioned considerations, the primary aims of this thesis were to characterise the breathing mechanics of UBE (Chapter 4), to explore the putative mechanisms that underpin the respiratory responses to UBE (Chapter 5), and assess whether UBE is sufficient to induce contractile fatigue of the respiratory muscles (Chapter 6). Detailed aims and objectives for each study are outlined after the *Literature Review* and in the respective experimental chapters.

Chapter Two

LITERATURE REVIEW

2-1 Introduction to Literature Review

The following literature review predicates the three experimental chapters presented in this thesis. The purpose of this section is to provide sufficient background theory and rationale for the current body of work. The review begins with a brief summary of the evolutionary adaptations that have occurred in the upper-body since the emergence of upright walkers, which ultimately influence the functional responses to exercise. A detailed discussion concerning the anatomical and physiological differences between UBE and LBE is then presented. The focus of the literature review then shifts to respiratory function in health and disease, and how this may be influenced by UBE. The chapter concludes with a summary of the mechanisms associated with, and the techniques used in the assessment of, respiratory muscle fatigue which is investigated in the final experimental chapter.

2-2 Upper-Body Structural Traits in Modern Man

Since humans developed bipedal gait, the structure of the upper-limbs has adapted to emphasise mobility and dexterity while reducing strength and stability. Such adaptations have been important for carrying, holding, manipulating objects and conducting fine motor tasks (Saladin, 2003). By contrast, the lower-limbs have adapted by stiffening and decreasing the joint range of motion in order to support the weight of the skeleton. Intense UBE is an activity, therefore, to which humans have not been historically conditioned, and physical tasks involving the upper-limbs result in the recruitment of additional thoracic muscles to aid in posture (Celli, 1988; Hodges *et al.*, 1997; Zedka and Prochazka, 1997; Hodges and Gandevia, 2000) and locomotion (Tortora and Grabowski, 2003). The additional loading of thoracic muscles during such upper-limb functions may restrict our usually versatile breathing patterns and influence respiratory mechanics. The following section provides an overview of the anatomical differences between the upper- and lower-body that likely influence many of the physiological responses to exercise.

2-2.1 The Evolution of Bipedal Locomotion

Bipedalism is a locomotory mode whereby an organism moves within an environment on two legs. Humans are alone among modern mammals in adopting bipedal gait (Bramble and Carrier, 1983). There is lack of consensus as to exactly when and why hominin bipedalism evolved, and the direct lineage is still under debate. It has been suggested, however, that bipedal locomotion evolved in humans from an arm-swinging (Morton, 1924; 1935, cf Harcourt-Smith and Aiello, 2004) and then a knuckle-walking (Washburn 1967; Richmond and Strait, 2000) ancestor. The latter supports the premise that the upper-limbs once played an important role in weight-bearing activities, after which there were drastic structural changes following the emergence of upright walkers. Bipedalism is likely a favourable evolutionary adaptation to food acquisition (Jolly, 1970) and/or provision carrying (Brace, 1962).

Transition within the human lineage towards bipedal locomotion resulted in a multitude of adaptive upper-body musculoskeletal traits. Observing modern monkeys and apes can provide an insight into how primates adapted to the arboreal (tree living) habitat and how certain human adaptations originated. For example, gorillas and chimpanzees have an additional rib in the dorsal vertebrae (Schultz, 1961), whereas the recent use of hominid upper-limbs in non-weight bearing tasks has led to the development of the cervical rib (Ohman, 1986), which is believed to be a modification of the first dorsal rib (Aiello and Dean, 1990). The cervical rib in humans is believed to be a consequence of an erect thorax (Stern and Susman, 1983) and freeing of the upper-limbs (Ohman, 1986). This anatomical structure is shared by *Australopithecus* and *Homo*

neanderthalensis; two early bipeds (Gea, 2008). Furthermore, while the human thorax has a characteristic barrel-shaped appearance containing 12 pairs of medio-laterally flattened ribs, the thorax of the great ape has a bell-shaped (inverted funnel) appearance (Beckman, 1973) and is elongated anteroposteriorly (Fig. 2-1) which affects respiratory mechanics (Schultz, 1961). By contrast, the human ribcage supports respiratory muscle mechanics that are more efficient for upright walking (Gea, 2008). Bipedal motion also resulted in compromised stability of the upper-limbs in favour of improved motility and manipulation (Moore *et al.*, 2010). The upper-limbs can grasp, strike, reach and conduct fine motor-skills more effectively than the lower, but are relatively less stable, and capable of modest strength and force development by comparison. For example, the pelvic (hip) and pectoral (shoulder) girdles are the two principal ball and socket joints in the lower- and upper-body, respectively. Yet, while the former comprises a bony ring (sacrum and hip-bone) in a deep ball and socket joint, the pectoral girdle consists only of the scapula, clavicle and humeral head in a shallow joint attached comparatively weakly by ligaments and tendons (Tortora and Grabowski, 2003). The result is a glenohumeral joint with high mobility but low stability that is more commonly injured than the hip with relatively less force application (Moore *et al.*, 2010). Collectively, these observations suggest that while human ancestors like the great ape have upper-limbs that function to bear-weight and brachiate, the human thorax and upper-limbs have devolved from weight-bearing tasks and, in its present form, is less compatible with heavy physical exertion. There may be both positive and negative implications of such chronic adaptations.

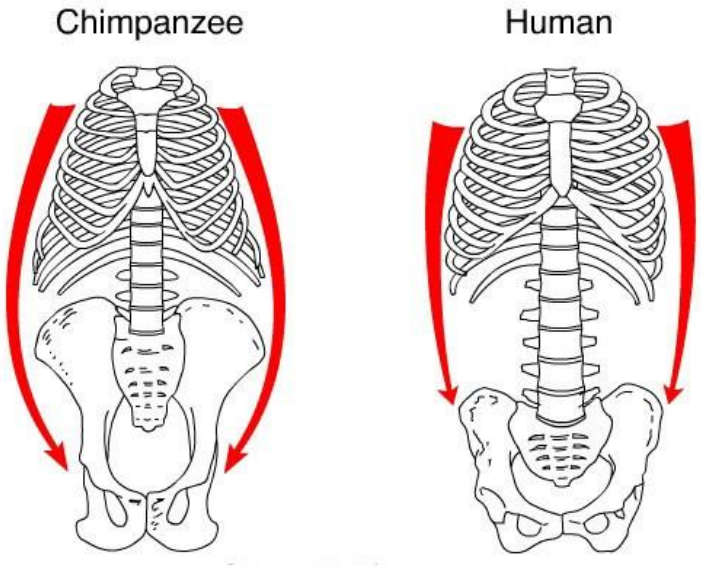

Fig. 2-1: The bell-shaped appearance of the early-ape ribcage (left) compared to the barrel-shaped appearance of the hominid rib cage (right). The structure of the thorax likely influences respiratory muscle orientation, size and strength and follows from the abstinence of humans from knuckle-walking.

An advantage of these chronic structural adaptations may be 'freeing' of the thoracic musculature to employ more versatile respiratory strategies during upright running. Locomotor-respiratory coupling (LRC, see below) is a form of breathing entrainment that refers to the phase-locking of locomotor and respiratory frequencies during exercise (Daley, Bramble and Carrier, 2013). Locomotor-respiratory coupling has been observed in a range of galloping quadrupeds (Iscoe, 1981; Simons, 1999; Bramble and Carrier, 1983) exhibiting a restricted stride/breath ratio of 1:1. By contrast, humans exhibit far greater flexibility in their entrainment strategies during running, with ratios of 2:1, 3:1, 4:1, 2:5:1 commonly used, or exhibiting no entrainment during which they will employ independent breathing and stepping frequencies (Bramble and Carrier, 1983; Banzett, 1992; O'Halloran; McDermott, Van Emmerik & Hamill, 2003). The versatility of human respiratory patterns relative to locomotion, likely relates to an upright posture and striding bipedal gait. Unlike in quadrupeds, the forelimbs (arms) are not subjected to impact loading or direct weight-bearing and, therefore, the forces transmitted through the thorax, abdomen and rib cage are relatively small. This reduces mechanical interactions between locomotion and ventilation. The benefit is that phase-locking respiratory and locomotor frequencies may facilitate respiratory flow, thus reducing the energy cost of breathing, and minimising antagonistic loading of the respiratory muscles (Daley, Bramble and Carrier, 2013). These favourable respiratory patterns in humans would not be possible without the prolonged abstinence from upper-limb impact loading, although it is currently unclear if humans exhibit less flexibility in their respiratory patterns during upper-limb loading tasks.

The potential disadvantage of chronic upper-body musculoskeletal adaptations to bipedal motion is a compromised ability for humans to perform strenuous locomotor tasks involving the upper-limbs, particularly when compared to the lower-limbs. Bony landmarks discovered on the fossils of early bipeds, e.g. Neanderthals, suggest that they had strong, powerful diaphragm muscles that were likely capable of generating respiratory pressures far exceeding that of modern man (Aiello & Dean, 1990). This may, in turn, have made early bipeds less susceptible to respiratory muscle fatigue, since increasing the strength of inspiratory muscles is associated with fatigue resistance in humans (Romer, McConnell & Jones, 2002a; Romer, McConnell & Jones, 2002b; Verges, Lenherr, Haner, Schulz & Spengler, 2007; Verges, Renggli, Notter & Spengler, 2009). By contrast, in response to a prolonged upright posture, modern humans have developed respiratory structures that are capable of modest pressure generation, moderate peak lung volumes, and respiratory muscles that exhibit contractile fatigue following high-intensity exercise (Johnson *et al.*, 1993; Mador *et al.*, 1993; Babcock *et al.*, 1995, 1996, 1998, 2002; Taylor *et al.*, 2006; Verges *et al.*, 2006). There is a cost attached to increases in upper-limb mobility; when humans revert to

heavy UBE, they exhibit postural and locomotor loading of the thoracic muscles to which they are not accustomed. Prior to rapid arm movements, there may be additional activation of the trunk muscles in order to stabilise the torso and maintain arm position (Celli, 1988; Hodges *et al.*, 1997), and there are phasic contractions of the superficial abdomen, diaphragm and erector spinae during repetitive arm movements (Hodges and Gandevia, 2000; Zedka and Prochazka, 1997). The combined ventilatory, postural and locomotor functions of the respiratory muscles are likely responsible for the altered breathing mechanics observed during UBE when compared to LBE (discussed below). Collectively, these insights suggest that the weak evolutionary pressure for humans to maintain the upper-limb strength and stability of our early ape (knuckle-walking) ancestors, has resulted in a compromised ability for humans to perform heavy tasks involving the upper-limbs.

Given the lineage of human bipedalism, it is possible that UBE places demands on the upper-body for which bipedal primates, e.g. *Homo neanderthalensis, Australopithecus* and *Homo sapian,* have not been conditioned since knuckle-walking, brachiating apes. As a result, the physiology of UBE differs considerably when compared to that of LBE; for a discussion of this topic, see *Upper- Versus Lower-Body Exercise: Physiology*. Prior to this, however, the following sections provide an overview of several key themes underpinning the thesis experimental chapters; specifically, the control of breathing, dyspnoea and locomotor-respiratory coupling.

2-3 The Control of Breathing

A central theme of this thesis pertains to the alternate methods by which humans ventilate the lungs when exercising with the upper- versus the lower-limbs. Specifically, this body of work explores how the locomotor mechanics of upper- and lower-body exercise influence the breathing patterns and mechanics of exercise ventilation (see *Respiratory Physiology*). Although the processes that underpin the ventilatory responses to physical activity are incompletely understood, it is thought that the central and peripheral feedback (and feed-forward) mechanisms that ultimately initiate and govern the control of breathing during exercise remain relatively unchanged across exercise modes. This section aims to provide a broad overview of the available literature concerning our current understanding of the control of breathing during exercise.

2-3.1 Introduction

Body cells depend on oxygen for energy transduction, which is regulated by the intracellular availability of adenosine triphosphate (ATP) (Tortora & Grabowski, 2003). Physical activity stimulates increases in ventilation to ensure that gas exchange at the lung matches that of tissue metabolism. In this way the organism can maintain respiratory homeostasis, i.e. meet cellular O_2 demand and eliminate CO_2 and H^+ from the blood. Pulmonary ventilation is achieved when contractions of the respiratory muscles induce changes in airway pressure to generate the required inspiratory and expiratory air flows. At rest, a basic respiratory rhythm generator induces phasic contractions of the respiratory muscles which are governed by central respiratory drive potentials that originate in the medulla (Sears, 1964). At exercise onset, energy demand is instantaneously increased, cell respiration is accelerated as a result and the basic respiratory rhythm generator is insufficient to maintain arterial O_2 content. A number of additional mechanisms, therefore, function to increase neural respiratory drive and ventilatory output. The mechanisms that underpin the exercise-mediated increase in $\dot{V}_E$ can be largely categorised into neural (feed-forward and feedback) and humoral (blood borne).

2-3.2 Rapid (Phase I) Exercise Hyperpnoea

The initial $\dot{V}_E$ response at exercise onset is considered too rapid to be mediated by an increase in circulating metabolites. As such, a feed-forward mechanism mediated by overarching cortical (neural) control of the respiratory centre has been proposed to explain this phenomenon; such feed-forward (pre-emptive) neural control refers to a signal generated in the brain that initiates hyperpnoea simultaneous with (or in advance of) locomotion (Forster *et al.*, 2012). The first empirical data to support the premise of a neurally-mediated control of $\dot{V}_E$ at exercise onset was

proposed by Krogh & Lindhard (1913). In their landmark study, they observed rapid changes in respiration that coincided with exercise onset, and concluded that ventilatory changes that occur with a latent period of <1 s cannot be associated with chemical changes which occur as a result of processes within working muscles. Such a ventilatory response must, therefore, be nervous in nature. Since this early research, a number of key papers have served to disambiguate our understanding of the neurally-mediated rise in $\dot{V}_E$ at exercise onset. For example, Asmussen & Nielsen (1964) reinforced the premise of a feed-forward influence on central neural drive at exercise onset. In a study on human subjects during which circulation to the legs was occluded using pneumatic cuffs, they found that a circulatory block (leg occlusion) did not attenuate the rapid rise in $\dot{V}_E$ following the onset of cycle exercise, suggesting a neurological control of $\dot{V}_E$ that was independent of a metabolic chemoreflex. Furthermore, Bell & Duffin (2006) observed a rapid increase in $\dot{V}_E$ following passive limb movement, suggesting that autonomic neural command had a degree of governance in the control of $\dot{V}_E$.

Such immediate and rapid neural control at exercise onset may be the result of mechanoreceptor feedback, which is initiated following increased activity of the locomotor muscles and pulmonary stretch receptors, the latter of which respond to rapid expansion of the lung and chest wall. Indeed, signals from pulmonary stretch receptors that mediate the respiratory centre control of inspiration is termed the Hering-Bruer reflex (West, 2005). Other mechanical receptors are known to exist in muscle spindles, Golgi tendon organs and skeletal joints, all of which send afferent signals to the sensory cortex which, in turn, relays information to the medullary respiratory centres. Dejours *et al.* (1957) were the first to propose the existence of mechanical receptors in skeletal muscle that function to stimulate pulmonary ventilation. In both awake and lightly anesthetised human subjects, Dejours *et al.* (1957) occluded venous return from the lower-limbs in order to negate the chemoreceptor-stimulated increase in pulmonary ventilation. Passive movement of the lower limbs resulted in elevated $\dot{V}_E$ without the accompanying increase in $\dot{V}O_2$ which would otherwise have indicated a change in muscle metabolism.

Given the density of sensory (afferent) nerves in the muscles and surrounding tissue, it is highly likely that muscle contraction stimulates activity of these receptors, contributing to neural feedback via spinal pathways (Forster *et al.*, 2012). Brain regions that stimulate the respiratory centres in response to mechanoreceptor afferents, include the cerebellum and the hypothalamus, the latter of which mainly exerts respiratory control following changes in body temperature (Brooks *et al.*, 2005). A majority of the nerve afferents (grouped I – IV) involved in afferent control of $\dot{V}_E$ comprise impulses from muscle spindles and Golgi tendon organs, which respond to

muscle stretch and distortion (Bessou, Dejours and Laporte, 1959), free nerve ending receptors in tendons (Paintal, 1960) and free nerve ending receptors in other locations including venous and lymph vessels and connective tissues. Furthermore, the speed with which afferent signals propagate spinal nerves to the respiratory centres is sufficient to account for the rapid increase in $\dot{V}_E$ at exercise onset (McCloskey and Mitchell, 1972).

Finally, behavioural and/or arousal state is also thought to influence the rapid $\dot{V}_E$ response at exercise onset. For example, although human ventilation increases significantly following the transition from rest to leg-extension exercise, the response is attenuated when participating in a cognitive task (puzzle-solving) at exercise onset (Bell, Feenstra and Duffin, 2005). Furthermore, ventilation increases at rest when exercise is imagined (Decety, Jeannerod, Durozard, & Baverel, 1993). Collectively, these data support the premise that central command has a primary role in regulating ventilation at exercise onset, and that autonomic activation in this context may serve to prepare the organism for action. Cumulatively, therefore, the phase I ventilatory response (i.e. an increase in $\dot{V}_E$ occurring simultaneously with exercise onset) is thought to be governed by arousal state and exercise anticipation, mechanoreceptor afferents in the muscles, tendons and ribcage, and neural feed-forward mechanisms that are mediated by descending suprapontine signals projecting to spinal locomotor and brainstem respiratory neurons (Forster *et al.,* 2012).

2-3.3 Slow (Phase II and III) Exercise Hyperpnoea

Where-as the phase I ventilatory response is concerned with the rapid and immediate rise in $\dot{V}_E$ following exercise onset, the phase II response, by contrast, is that which occurs during exercise when $\dot{V}_E$ increases to steady-state and is sufficient to meet the demands for metabolic gas exchange (West, 2005). Furthermore, the phase III response is associated with the *fine tuning* of $\dot{V}_E$ via peripheral sensory feedback mechanisms and is independent of feed-forward control (McArdle, Katch & Katch, 2000). These processes are governed by both central neural command and metabolic control. The motor cortex is situated above the pons and is, therefore, said to exert 'suprapontine' control over ventilation. The motor cortex is jointly responsible for stimulating the respiratory centre to achieve the elevated ventilatory rates necessary for exercise, in addition to the *voluntary* control of breathing and the integration of respiratory and locomotor patterns (Brooks *et al.,* 2005). As such, the cortex likely has an essential role in regulating breathing during upper-body dependent activities that require some degree of voluntary control over the respiratory breath, e.g. swimming, weight-lifting and tasks which require a high degree of respiratory-locomotor entrainment. Because of the predominance of signals from the motor cortex and other higher brain regions in governing breathing during exercise, some authors (e.g.

Mitchell, 1990) suggest that breathing during exercise is predominantly under central command. In addition to the motor cortex, other areas that facilitate the medullary respiratory centre include the hypothalamus, cerebellum and the reticular formation (Brooks *et al.,* 2005). Few data exist on the output of the cortical area to the respiratory centre during exercise in humans, primarily due to the invasive procedures necessary to make such measurements, and much of the research has been limited, therefore, to animal models. In one such study investigating central control of $\dot{V}_E$, Eldridge, Millhorn, Killey, & Waldrop, (1985) studied the ventilatory responses to electrical and chemical stimulation of the feline hypothalamus. The cats were anaesthetised and paralysed, and the phrenic and bicep femoris nerves monitored for ventilatory and locomotor responses, respectively. Ventilatory responses were similar to those observed from spontaneous or evoked locomotion, i.e. an increase in $\dot{V}_E$ despite lack of humoral control. As such, central command exerts its substantial influence on $\dot{V}_E$, at least in part, via hypothalamic control.

There is emerging evidence that the role of central command in the control of central motor drive and exercise hyperpnoea is also likely influenced by a reflex response from working muscle, specifically, group III and IV muscle afferents. Initial studies investigating this phenomenon used local anaesthetics (lumbar epidural space) to block the central projection of group III/IV muscle afferents during whole-body endurance exercise. Following administration of the anaesthetic, cardiovascular and ventilatory function during exercise increased, decreased and remained unchanged compared to placebo (Freund, Rowell, Murphy, Hobbs & Butler, 1979; Friedman, Brennum, Sztuk, Hansen, Clifford *et al.*, 1993; Smith, Querry, Fadel, Gallagher, Stromstad *et al.*, 2003). These contradictory findings were likely due to the type of anaesthetic used, i.e. local epidural anaesthetics, which attenuate efferent as well as afferent nerve activity, resulting in a drug-induced muscle weakening (Amann, Proctor, Sebranek, Eldridge, Pegelow *et al.,* 2008). Several contemporary studies, however, circumvent these methodological issues by using intrathecal fentanayl, a selective l-opioid receptor agonist, to inhibit the central projection of group III/IV muscle afferents without affecting the muscle's force-generating capacity, central motor drive or feed-forward control (Amann, 2012). Importantly, the authors controlled for a direct central effect of fentanyl by documenting unchanged resting cardiorespiratory responses. When muscle afferents were blocked during cycle exercise across a range of intensities, central motor drive, circulation and pulmonary ventilation were substantially compromised (Amann, Blain, Proctor, Sebranek, Pegelow *et al.,* 2010; Amann, Runnels, Morgan, Trinity, Fjeldstad *et al.*, 2011). The result was a reduction in perfusion pressure and blood flow, resulting in arterial hypoxaemia, and ventilatory and metabolic acidosis. A later study demonstrated the negative influence of these factors on exercise capacity, in addition to facilitated peripheral locomotor

muscle fatigue during exercise (Amann, Blain, Proctor, Sebranek, Pegelow *et al.*, 2011). Collectively, these studies suggest that that continuous sensory feedback from working skeletal muscles may have a principal role in controlling central motor drive and ventilatory responses during exercise.

Humoral input to the cortex, however, is also an essential cog in the feedback process that regulates the slow phase of the ventilatory response to prolonged physical activity. Exercise increases cell metabolism and the production of CO_2 which is buffered by the bicarbonate pool. At exercise intensities above the gas exchange threshold, CO_2 and H^+ production increase exponentially due to the insufficient buffering of CO_2 by carbonic acid, affecting blood concentrations of PO_2, PCO_2 and pH (Tortora & Grabowski, 2003). Specialised cells on the ventral surface of the medulla are sensitive to both changes in H^+ concentration and the pH of the medullary interstitial or cerebrospinal fluid (CSF), the latter of which appears to be more affected by changes in $PaCO_2$ (Brooks *et al.*, 2005). Indeed, CSF with its low buffering capacity is sensitive to H^+ ions that accumulate (as a result of high exercise work rates) and then diffuse across the blood brain barrier. This process separates the CSF and arterial blood, resulting in the additional formation of carbonic acid and a further drop in pH (Brooks *et al.*, 2005). Among the first to propose a humoral mechanism for the control of breathing during exercise, beyond the initial rapid response, were Zuntz & Geppert (1886; cf Forster *et al.*, 2012), who suggested that substances in the circulating blood were responsible for stimulating exercise hyperpnoea. Empirical data was later presented by Haldane & Priestly, (1905) suggesting the important role of $PaCO_2$ and PaO_2 in the regulation of breathing. This instigating research formed the basis of our current understanding, and stimulated further interest into the influence of CO_2 production on exercise hyperpnoea.

The contemporary literature suggests that chemoreceptors play an important role in the regulation of exercise ventilation. Chemoreceptors are situated in the common carotid, aortic and brachiocephalic arteries which send afferent signals to the medullary respiratory centre in response to changes in metabolic status. Tightly regulated ventilatory mechanisms during exercise mean that rarely do the carotid bodies detect changes in arterial PO_2 or PCO_2; as such, any contribution of the carotid bodies to ventilatory drive are thought to result from a decrease in pH (Brooks *et al.*, 2005). The aortic bodies, however, are considerably more sensitive to decreases in PaO_2 and pH, in addition to increases in $PaCO_2$. Ventilatory drive is so closely linked to $\dot{V}CO_2$ that many have hypothesised the existence of additional peripheral chemoreceptors in the right heart, pulmonary artery or the lung itself, but efforts to demonstrate

this empirically have thus far proved unsuccessful. A key study in furthering our knowledge of chemoreceptor location was conducted by Hildebrandt *et al.* (1979) who assessed the association of CO_2 flux with exercise ventilation. Their participants performed cycle ergometry while wearing pressure cuffs on the lower-limbs which functioned to occlude venous return. Following release of the cuff there was a delay of 5 - 10 s as the CO_2 trapped in the legs reached the lungs, after which there was an increase in end-tidal PCO_2 ($P_{ET}CO_2$). Ten – eighteen seconds later there was an increase in $\dot{V}_E$ due to the time taken for the increased CO_2 load to reach and stimulate the arterial chemoreceptors, thus affecting pH. As a result, the study was able to confirm the arterial chemoreceptor influence on $\dot{V}_E$. Furthermore, their data led to the widespread rejection of the hypothesis that pulmonary chemoreceptors influence the ventilatory response as, had this have been the case, $\dot{V}_E$ would have been elevated concomitantly with $P_{ET}CO_2$.

Despite a great deal of research into the humoral control of $\dot{V}_E$, the pursuit of a single mediating mechanism combined with the many incompatible experimental methodologies used in early research, has resulted in contradictory mechanisms being proposed and a lack of consensus in the literature. Indeed, a number of theories have been proposed to explain the humoral control of ventilation including: an increased respiratory centre sensitivity to H^+ ions (Krogh & Lindhard, 1913), increased receptor activity in response to changes in airway CO_2 (Bartlett & Sant' ambrogio, 1976), increased receptor activity in response to pulmonary blood CO_2 (Sheldon and Green, 1982; Huszczuk, Whipp, Oren, Shors, Pokorski *et al.*, 1986), attenuated vagal feedback (Bartlett & Sant' ambrogio, 1976), and cardiac afferent mediation (Jones, Huszczuk & Wasserman, 1982; Lloyd, 1984). Contemporarily, the 'neuro-humoral theory' (Dejours, 1964) is accepted as our most comprehensive explanation for the control of breathing during exercise, suggesting that exercise hyperpnoea is mediated by a combination of both central neural command and humoral control, both of which pertain to multiple mechanisms.

2-3.4 Conclusions Regarding the Control of Breathing

The large and abrupt increase in ventilation that occurs as exercise starts and continues has been a difficult phenomenon for scientists to comprehensively explain. At exercise onset, muscle and joint nerve afferents, as well as neural input from the motor cortex, increase output to the respiratory centres to elevate $\dot{V}_E$. As exercise persists, however, descending neural output is mediated jointly by central command and humoral controls, and the neuro-humoral theory of Dejours (1964) provides the most likely explanation of this phenomenon to date. At exercise cessation, cortical and neural input to the respiratory centres cease and $\dot{V}_E$ is dramatically reduced. Ventilation remains relatively high post-exercise, however, until humoral disturbances eventually

diminish. The specific mechanics of ventilation and the degree to which descending neural output is met with an appropriate mechanical response at the lung is governed by a number of factors including respiratory health and exercise mode.

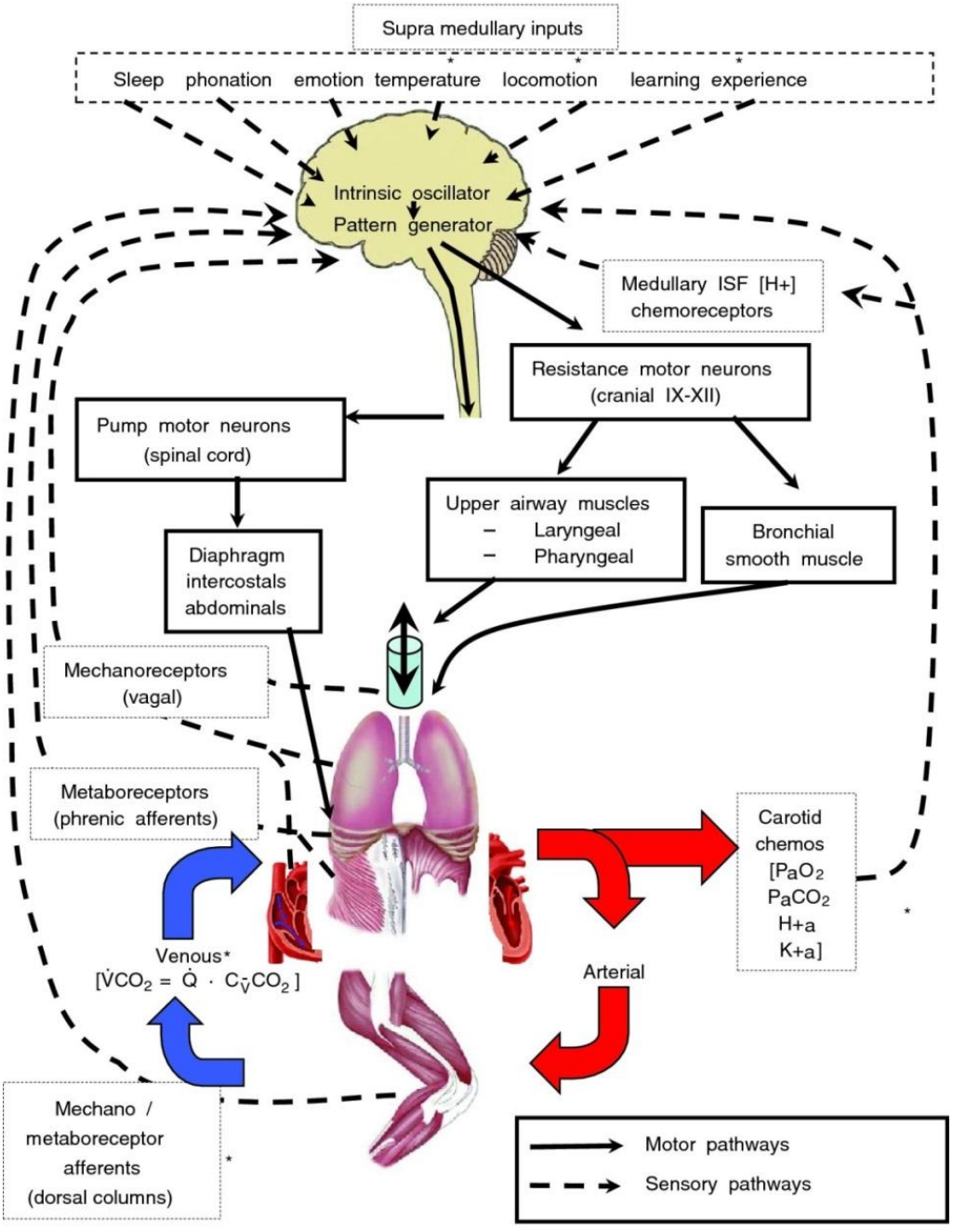

Fig. 2-2: Schematic depicting multiple structures contributing to the control of breathing; see text for detailed description. Figure from Dempsey *et al.* (1985).

2-4 Dyspnoea

Dyspnoea has been defined as a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity (Parshall, Schwartzstein, Adams, Banzett, Manning *et al.,* 2012). As such, dyspnoea may be experienced during exercise by trained athletes, in addition to untrained or unhealthy individuals during ambulation or tasks of everyday living. Chapters 5 and 6 of this thesis make quantitative measures of dyspnoea using the Borg modified CR10 scale (Borg, 1998) to interpret subjective ventilatory stress during arm-cranking performed at various exercise intensities and cadences. As such, this section provides a discussion of the various definitions and classifications of dyspnoea, and presents a broad summary of the underlying neurophysiology. Due to the considerable volume of available literature pertaining to dyspnoea, only the pertinent studies will be highlighted.

2-4.1 Unifying Definitions

The American Thoracic Society (2012), in their statement on the causative mechanisms and assessment of dyspnoea, state that the experience of breathlessness is concerned with interactions among multiple physiological, psychological, social and environmental factors. However, the multitude of subjective and objective factors that predicate the individual response result in poor agreement between studies both in the way it is utilised as a tool and how it is explained/described to study participants. The ATS guidelines have long been the authority on respiratory assessment techniques and position stands, and although their definition acknowledges the complexity of the perceptual dyspnoeic response, the most widely applied measures of dyspnoea do not. Several systematic reviews note that the number and diversity of dyspnoea measures makes it difficult to synthesise a comprehensive critique (Bausewein, Farquhar, Booth, Gysels & Higginson, 2007; Johnson, Oxberry, Cleland & Clark, 2010). Furthermore, while some authors have endeavoured to unify the quantification of breathlessness in various conditions and populations using both qualitative (Simon, Schwartzstein, Weiss, Lahive, Fencl *et al.,* 1989; Simon, Schwartzstein, Weiss, Fencl, Teghstoonian *et al.,* 1990) and quantitative (Borg, *et al.,* 1998; 2010) assessment scales, others have modified these scales (O'Donnell *et al.,* 2000; Han *et al.,* 2008; Smith *et al.,* 2009; Meek *et al.,* 2012) making comparisons across the literature problematic.

The definitional ambiguity of dyspnoea across previous studies, and variability in the interpretation of such definitions by participants, present the main problem in coordinating a consensus on the perceptual responses to exercise. Furthermore, although the modified Borg CR10 scale and the visual analogue scale (VAS) are the most commonly used scales in quantifying the degree of dyspnoea (Mador *et al.,*1995), it is also the perceptual qualitative

descriptors that change, and a variety of disparate expressions including 'chest tightness' and 'out of breath' have been used (Simon *et al.*, 1989). In a study into the perceptual responses of healthy participants to incremental cycling exercise, Borg *et al.* (2010) asked their volunteers to give 'ratings of breathlessness' using the modified CR10 scale. Using the same scale with similarly aged men, O'Donnell *et al.* (2000) asked participants to rate 'the intensity of perceived breathing discomfort.' To further complicate subjective interpretation of the perceptual measures, this latter study defined dyspnoea as 'difficulty breathing.' The ATS statement on dyspnoea (ATS, 2012) suggest that definitions of dyspnoea should avoid use of terms such as 'difficult', 'laboured' or 'heavy' as these are themselves descriptors of sensory experience and may result in the prior anticipation of subjective ratings. Other investigators have operationally defined dyspnoea as the 'effort to breathe' (Silverman, Barry, Hellerstein, Janos, & Kelsen, 1988; Muza, Silverman, Gilmore, Hellerstein, & Kelsen, 1990). However, Mador *et al.* (1995) established that exercising COPD patients were unable to discriminate (in a quantitative fashion) between the sense of 'effort to breathe' and the degree of 'respiratory discomfort', suggesting that either of these two definitions may be appropriate. It is worth noting that the quality of the sensation of dyspnoea in patients with COPD is likely to be quite different from that experienced by healthy people, with the former often reporting "unsatisfied inspiration" following the inflection (or plateau) of the V_T response during exercise (Laveneziana, Webb, Ora, Wadell & O'Donnell, 2011). Collectively, these data suggest that despite poor agreement between studies, there may be a broad range of definitions and methods of quantification that are appropriate for use in both health and disease, but that the qualitative descriptors should be kept consistent within a given population. The actual definition used should remain neutral with respect to any particular quality (ATS, 2012).

There is also discrepancy in the way researchers have assessed the qualitative sensory aspects of dyspnoea. A pair of studies by Simon *et al.* (1989; 1990) attempted to unify the sensory descriptors of dyspnoea in both healthy participants and patients with shortness of breath. Dyspnoea was induced using a range of stimuli (breath holding, CO_2 inhalation, volitional ventilation, resistive loading, elastic loading, imposed pattern of breathing and high inclined treadmill walking) and participants were asked to choose from a range of descriptors that were most applicable to their subjective experience. The study outcome was a comprehensive list of 19 qualitative dyspnoea descriptors, subcategorised into *rapid, exhalation, concentration, shallow, work, suffocating, hunger, heavy* and *gasping.* A separate list was developed for patients exhibiting shortness of breath, with the main difference being the inclusion of a category for '*unsatisfied inspiration'.* In a study using chest wall restriction and deadspace loading in healthy men, O'Donnell *et al.* (2000) modified the original list by removing descriptors associated with

gasping but without subsequent explanation. Recognising that dyspnoea research is lacking consistency in the measurement of different qualitative aspects of respiratory discomfort, Meek *et al.* (2012) developed the Multidimensional Dyspnoea profile (MDP) as an instrument designed to assess the sensory and affective dimensions of dyspnoea. In the hope of unifying the sensory assessment of breathlessness, the MDP consists of 5 sensory qualities and 5 emotional responses, each of which has the potential to vary independently from one another. Despite their study reporting strong intraclass correlation for the measures used, few authors have implemented the MDP in subsequent experiments.

There is definitional ambiguity and variability in perceptual scales used in the existing literature pertaining to dyspnoea, and studies have not yet validated a single definition or measurement scale as having greater efficacy over another. In consideration of the available literature, however, this thesis uses the most commonly referenced contemporary terms and definitions and describes dyspnoea to participants as 'the intensity of breathing discomfort'. Since both the modified Borg CR10 scale and visual analogue scales are widely used and validated, participants in the following experimental chapters will be asked to rate their perceptual responses on the modified Borg CR10 scale (Borg, 1998), since a majority of the volunteers are students on the sports science undergraduate degree course, and will be familiar with such scales. Furthermore, the end points of the scale are anchored such that zero represents 'no breathing discomfort' and 10 represents the 'maximum breathing discomfort you have experienced or could imagine experiencing.' Pilot testing for each experimental chapter in this thesis indicated that the length of time required for participants to complete the *qualitative* questionnaires was incompatible with the various testing protocols. As such, the decision was made not to assess the different *sensory descriptors* of dyspnoea.

2-4.2 The Neurophysiology of Dyspnoea

Dyspnoea is the subjective perception of breathlessness, while the symptoms associated with dyspnoea result from the conscious recognition and interpretation of sensory stimuli and their meaning. The sensory afferents responsible for respiratory sensation have been discussed previously (see *The Control of Breathing*) and include feedback from carotid and aortic bodies, medullary chemoreceptors, slowly and rapidly adapting pulmonary stretch receptors, various fibres in the lung and airway, and tendon organs and spindles in the respiratory pump muscles (ATS, 2012). There may also be sensory feedback on the state of respiration from respiratory motor areas of the brain which results in descending motor activity via corollary discharge to

perceptual areas. Relatively less is known, however, about how this sensory information activates regions of the cerebral cortex to produce the perceptions of dyspnoea.

In terms of respiratory work and/or effort, it is generally accepted that respiratory muscle afferents project to the cerebral cortex, and that participants report sensations localised to the respiratory muscles when the work of breathing is high (Gandevia & Macefield, 1989). However, breathlessness has also been positively associated with the intensity of inspiratory pressure (Poe), the frequency of breathing, the inspiratory duty cycle (representative of the velocity of shortening) (El-Manshawi, Killian, Summers, & Jones, 1986) and tidal volume constraints (Laveneziana *et al.*, 2011). The neurophysiological mechanism purported is a conscious awareness of the intensity of the outgoing motor command by means of corollary discharge within the central nervous system (El-Manshawi *et al.,* 1986). As such, perceptions of work and effort likely arise through a combination of respiratory muscle afferents and perceived cortical motor command or corollary discharge. The sensations of breathing discomfort, however, remain tolerable during exercise as long as ventilation is sufficient to meet metabolic demand. Under these circumstances, afferent mechanoreceptor feedback indicates that the ventilatory output is appropriate and proportionate to the descending respiratory drive (Jensen, Ofir & O'Donnell, 2009; Scano, Innocenti-Bruni & Stendardi, 2010), and respiratory sensations are rarely the primary reason for exercise cessation. The perception of breathing effort or work, however, is increased during exercise and can be artificially augmented with external resistive or elastic loads (Simon *et al.,* 1989), volitional hyperpnoea (Killian, Gandevia, Summers & Campbell, 1984), or by weakening the respiratory muscles with pre-fatiguing procedures (Gandevia, Killian & Campbell, 1981). In such instances, the required motor command and corollary discharge is increased, likely exacerbating sensations of respiratory effort (El-Manshawi *et al.,* 1986). Furthermore, if a poor effort/displacement ratio is observed (i.e. if corollary discharge and respiratory effort increase independently of increases in $\dot{V}_E$), as is often the case in COPD, activation of central limbic structures may form the basis for distressing respiratory sensations and elevated perceptions of dyspnoea (Mahler & O'Donnell, 2005). In people with obstructive lung disease, the discrepancy between efferent drive and afferent feedback is exacerbated by a greater brain-stem drive to breathe, coupled with increased airflow resistance, alterations in chest wall geometry, EFL and dynamic hyperinflation; the result is an increased intensity of dyspnoea (McConnell, 2013) and a reduced exercise tolerance (ATS, 2012).

Further discussion is warranted as to how sensory nerve afferents are collectively interpreted by the individual as a series of distressing respiratory symptoms. Partial explanations for this phenomena come from studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to infer neural activation from changes in cerebral blood flow (for review of techniques, see Evans, 2010). Initial PET studies by Banzett, Mulnier, Murphy, Rosen, Wise *et al.* (2000) found that air hunger, induced with constant mild hypercapnia, resulted in strong activation of the right anterior insular cortex. Using dyspnoea-inducing restricted ventilation, Evans, Banzett, Adams, McKay, Frackowiak *et al.* (2002) imaged the entire brain using fMRI. They too observed anterior insular activation, but found additional activation of both limbic and paralymbic structures, as well as the midline cerebellar (Fig. 2-3). Such localised cerebral activation is similar to that observed following the induction of somatic pain (Price, 2000; 2002). The only study to induce both respiratory discomfort (via inspiratory loading) and peripheral pain (via skin heating) in the same subjects, failed to differentiate the location of brain activation between the two sensations (von Leupoldt, Sommer, Kegat, Baumann, Klose *et al.*, 2009). Collectively, these data suggest that laboratory-induced dyspnoea results in the activation of cerebral structures that also serve to exacerbate subjective awareness of pain. The shared dyspnoeic and pain-induced activation of cerebral structures, in addition to the early detection of stimuli signalling threat to an organism, may provide an evolutionary advantage since the perception of aversive bodily sensations (e.g. dyspnoea and pain) likely motivates fast adaptive behaviour, thus ensuring survival (von Leupoldt *et al.*, 2009).

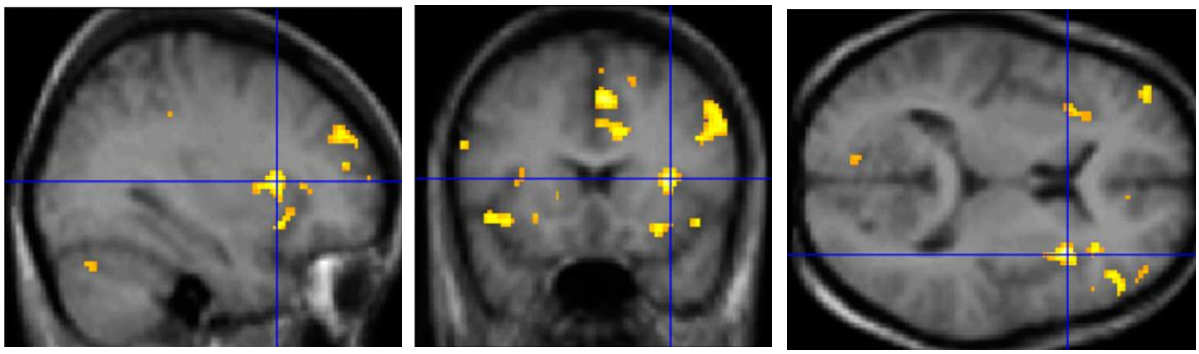

Fig. 2-3: Functional magnetic resonance imaging showing cerebral activations correlated with the experience of strong air hunger in healthy subjects. Strong activation is shown in the right interior insula, but also left anterior insula, anterior cingulate, supplementary motor area, prefrontal cortex and cerebellum. Most regions are categorised as limbic/paralymbic, and overlap with activations seen with pain, thirst, fear and hunger (Evans *et al.*, 2002).

2-4.3 Conclusions Regarding Dyspnoea

There has been dramatic progress in research into the mechanisms that underpin the dyspnoeic response, although the scientific understanding of the causes of dyspnoea is incomplete. Furthermore, there is widespread disagreement on the operational definitions and the methods used in both qualitative and quantitative measurement. This is hampered further by lack of consistency between studies. People with obstructive lung disease exhibit specific pathology that results in differences in the sensory perceptions of dyspnoea when compared to healthy individuals. As such, measurement scales and qualitative descriptors should perhaps be tailored to each population. Further research and critical review of the available literature is needed to unify the various definitions and measurement techniques.

2-5 Locomotor-Respiratory Coupling

Chapter 5 makes a quantitative comparison of the prevalence of locomotor-respiratory coupling (LRC) during arm-cranking across various work rates and cadences. Locomotor-respiratory coupling is a form of breathing entrainment that refers to the phase-locking of locomotor and respiratory frequencies during exercise (Daley, Bramble and Carrier, 2013). During periods of entrained breathing, ventilation frequency is 'entrained' to a sub-harmonic of the exercise rhythm (Paterson, Wood, Morton & Henstridge, 1986), and individuals time their respiratory cycle to occur at a specific phase of the locomotor cycle. Although humans entrain their breathing during upright ambulation (Daley *et al.*, 2013), it is likely that when loads through the torso exacerbate the mechanical demands of the respiratory muscles, such as during dynamic upper-limb exercise, participants may engage in LRC in order to simplify the coordination of respiratory and postural tasks (Hodges *et al.*, 2001). Such entrainment may be useful as it reduces mechanical interactions between locomotion and ventilation which minimises the conflict between muscles that contribute to both (Carrier 1991; Deban and Carrier, 2002). As a consequence, entrainment may facilitate respiratory flow, thus reducing the energy cost of breathing and minimising antagonistic loading of the respiratory muscles (Daley *et al.*, 2013). Locomotor-respiratory coupling has been observed in a range of mammals, humans included. In galloping quadrupeds, high impact forces associated with ground-striking are transmitted through the thoracic complex, and restrict the stride/breath ratio to 1:1 (Iscoe, 1981; Simons, 1999; Bramble and Carrier, 1983). By contrast, the human forelimbs (arms) are not subjected to impact loading or direct weight-bearing during most tasks and, therefore, the forces transmitted through the thorax, abdomen and rib cage are relatively small. This enables humans to exhibit far greater flexibility in their entrainment strategies during running, with ratios of 2:1, 3:1, 4:1, and 2:5:1 commonly used, or often exhibiting no entrainment during which they employ independent breathing and stepping frequencies (Bramble and Carrier, 1983; Banzett, Mead, Reid & Topulos, 1992; O'Halloran, Hamill, McDermott, Remelius & Van Emmerik, 2012).

The early research into breathing entrainment focused on the prevalence of entrainment during a range of exercise tasks, although various methods were used in quantifying the phenomenon. Bechbache & Duffin, (1977) assessed entrainment during cycling and treadmill running using cross-correlation to detect relationships between trains of respiratory and locomotor impulses. The authors made two interesting observations: 1) there was a greater tendency for individuals to entrain during cycling exercise at higher cadences compared to lower cadences; and 2) individuals entrain more often during treadmill running compared to treadmill walking. The findings were attributed to the severity of the exercise, the frequency of movement, the degree of fitness of the

volunteer, whether or not steady state had been achieved and the degree of familiarity with the exercise testing procedure. In their study, however, Bechbache & Duffin, (1977) used a metronome as a stimulus for exercise rhythm which could confound the data since participants may have entrained with the auditory cue rather than exclusively with the locomotor frequency. In the only study to date to compare cycling and arm-cranking, Paterson, Wood, Morton & Henstridge, (1986) assessed the tendency of their volunteers to entrain based on the premise that, during rhythmic exercise, breathing frequency exhibits an integer-multiple relationship to limb movement. Ratios of limb frequency to dominant respiratory frequency were determined, and data that lay within ± 0.05 of an integer or half-integer ratio were accepted as indices of entrainment, provided that the observed entrained scores were statistically significant. In their study, the tendency to entrain was minimally greater during bicycle ergometry, and was attributed to task familiarity. There may also have been an influence of ventilatory output on the prevalence of entrainment, since exercising $\dot{V}_E$ was not matched between modes. The following year, the same research group assessed the incidence of entrainment during exercise in hypoxia, and found that entrainment decreased linearly with decreasing atmospheric O_2 content (Paterson, Wood, Marshall, Morton & Harrison, 1987). This interesting observation was most likely associated with a hypoxia-induced hyperpnoea which dissociated respiratory frequency from stride rate, the latter of which did not change. These early studies demonstrated empirically that exercise rhythm may have a regulatory role on the control of breathing during moderate, rhythmical exercise. However, the range of techniques used in the assessment of entrainment throughout these early studies make it difficult to formulate a consensus on the tendency for humans to entrain during exercise.

Contemporary studies have more closely associated antagonistic loading of the thoracic musculature with the tendency to entrain. A review by Bramble and carrier (1983) highlighted that the upright posture of therian mammals comprises a support mechanism in which the anterior trunk is suspended by a muscular sling attaching the forelimbs to the ribs and sternum. During locomotion, therefore, the thoracic complex is cyclically loaded. Furthermore, since many axial muscles of vertebrates contribute to both breathing and locomotion (Carrier, 1991; Hodges & Gandevia, 2000a), it is thought that active inspiration is most compatible with a specific and different phase of the locomotor cycle than active expiration. This notion was demonstrated empirically by Daley *et al.*, (2013) who measured locomotor-ventilatory dynamics in 14 adults running at a self-selected speed. The study participants naturally preferred LRC patterns that minimised antagonistic interactions and aligned ventilatory transitions with phases of the locomotor cycle (step) that assisted rather than impeded respiratory flow. Indeed, ventilatory transitions initiated in 'preferred' phases within the step cycle occurred twice as fast as those

initiated in 'avoided' phases (Fig. 2-4). The authors hypothesised that humans coordinate breathing and locomotion in an effort to minimise antagonistic loading of respiratory muscles. Since these responses occur during upright ambulation, it is likely that exercise involving more direct loading of the thoracic complex would exacerbate the need to phase-lock the locomotor and respiratory cycles, and yet research in this domain is lacking.

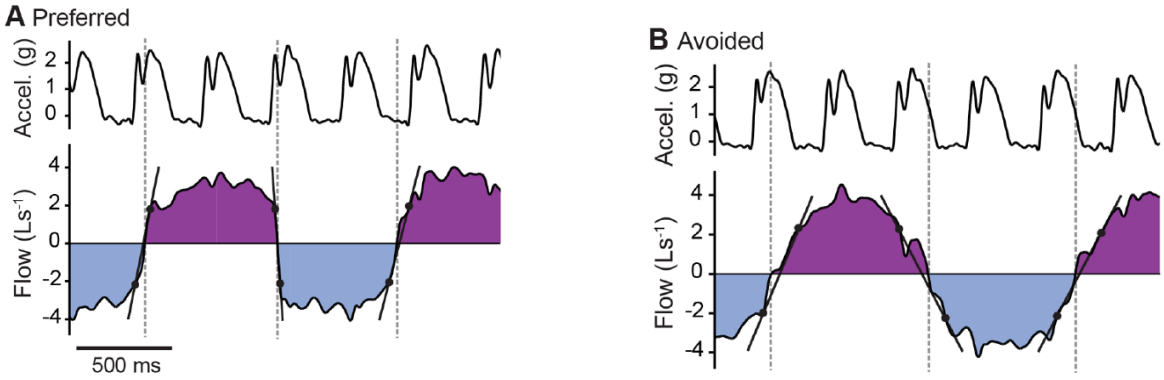

Fig. 2-4: Phasing of steps relative to breaths has a significant effect on the duration of ventilatory transitions. Panel A represents ventilatory transitions timed with preferred and assistive phases of the step cycle, facilitating rapid transitions. Panel B represents transitions timed with an avoided and antagonistic phase of the step cycle. Dashed vertical lines indicate zero-crossings of ventilatory transitions (Daley *et al.*, 2013).

There are several instances in which dynamically exercising humans are more likely to entrain their respiratory and locomotor frequencies. During rowing, the presence of a clear power stroke during which the agonist muscles forcefully contract, followed by the subsequent recovery phase, necessitates that athletes entrain their respiratory cycle to occur at a point in the locomotor cycle that minimises obstructions to respiratory flow. In the context of rowing, this would usually result in an expired breath during the power stroke, and an inspired breath during the recovery phase, regardless of the f_R. Early research in this domain suggested that the ability to entrain during rowing may be associated with training status. Mahler, Shuhart, Brew & Stukel, (1991) compared the entrainment patterns of elite, sub-elite and untrained rowers. They found that while the elite rowers exhibited similar ratios of respiratory and stroke frequencies, the ratios varied among the less well-trained, suggesting that task familiarity and experience aid in the ability to entrain. Steinacker, Both & Whipp, (1993) also assessed the pulmomechanical and breathing pattern features of rowing-induced hyperpnoea in elite rowers and found entrainment in all participants, exhibited by the tendency for stroke frequency and respiratory frequency to increase concomitantly. Furthermore, since dynamic airway compression occurred during exhalation at high work rates, thus constraining V_T, the necessity to increase the f_R may have resulted in the tendency to entrain stroke and respiratory frequencies. Finally, contrary to the earlier studies by Paterson *et al.* (1987), the tendency for rowers to entrain the respiratory and locomotor frequencies was not significantly different between constant-power exercise performed in normoxia and hypoxia, despite greater $\dot{V}_E$ and f_R in the latter (Fabre, Perrey, Passelergue & Rouillon, 2007). Collectively, these data suggest that there is an overarching mechanically-mediated control of respiratory entrainment patterns during rowing, possibly associated with dynamic use of the upper-limbs, patterns which are also likely influenced by task familiarity. Furthermore, the mechanical influence of rowing locomotion on entrainment likely supersedes any influence of hypoxia.

2-5.1 Conclusions Regarding Locomotor-Respiratory Coupling

Locomotor-respiratory coupling has received much literary attention in the context of animal models and entrainment patterns during upright human ambulation. The available data suggest that LRC is initiated when additional loading of the thoracic complex results in heightened conflict for the ventilatory and postural functions of the respiratory muscles. Although initial studies of LRC focussed on the frequency of entrainment in the context of exercise mode or cadence rate, the contemporary data closely associates entrainment with thoracic muscle loading and the need to coordinate the respiratory cycle with a mechanically compatible phase of the locomotor cycle. Locomotor-respiratory coupling is a poorly studied area of human respiratory

physiology, particularly in the context of UBE. Further studies in this domain may provide important insights into the mechanically-mediated influence of locomotor function on respiratory patterns and mechanics.

2-6 Upper- Versus Lower-Body Exercise: Physiology

There are three predominating anatomical characteristics that explain the differences in exercise responses between the upper- and lower-body: 1) differing potential to generate muscular tension, due to the absolute volume of active muscle and muscle cross-sectional area; 2) differences in oxidative capacity due to a disparity in fibre-type distribution and recruitment patterns; 3) differences in the perfusion capacity of upper- and lower-body skeletal muscles, dictated by capillary density, differences in vascularisation and intramuscular pressures (Sawka, 1986). Several authors investigating the physiological (Davies and Sargeant, 1974), haemodynamic (Blomqvist *et al.*, 1981) and ventilatory (Sawka *et al.*, 1982) responses to arm exercise suggest, however, that the principal cause underpinning the differences in physiological function between arm and leg exercise is the smaller skeletal mass involved in the former. Although both modes of exercise engage the same respiratory muscles, the recruitment patterns are different, and there are reports that the postural roles of the respiratory muscles are exacerbated during UBE (Celli, 1988; Hodges *et al.*, 1997; Hodges and Gandevia, 2000; Zedka and Prochazka, 1997). There are virtually no exercise tasks performed by able-bodied populations that exclusively utilise the arms, shoulders and chest muscles without subsequent recruitment of the thorax, pelvic or lower-limb muscles to aid in posture. A vast majority of research assessing the physiological responses to arm-crank exercise have not restrained the torso of exercising participants (Sawka, 1986), which allows for the active recruitment of the back, shoulders and thoracic muscles to aid in locomotion. The volume of active mass involved in such exercise tasks is, therefore, difficult to predict which makes direct comparisons between upper- and lower-body exercise problematic.

Despite uncertainty regarding the absolute volume of muscle mass involved in upper- versus lower-body exercise, there is more agreement with regards to the type of muscle recruited, and this can equally affect exercise capacity and cardiorespiratory function. The available literature suggests that the proportion of type-I muscle fibres in the upper body (arms, chest and shoulders) is significantly lower than that in the lower body (legs and gluteals) and comprises ~30% and ~50% of upper- and lower-body fibres, respectively (Susheela and Walton, 1969; Gollnick *et al.*, 1972; Johnson *et al.*, 1973). Furthermore, the arms have a greater proportion of type-II fibres when compared to the legs in the same participants (Johnson *et al.*, 1973; Turner *et al.*, 1997). This results in greater type-II muscle fibre recruitment during upper-body tasks (Kang *et al.*, 1997; Xu and Rhodes, 1999), which predicates many of the differences in physiological function between UBE and LBE. This section provides an overview of such physiological differences, with respect to the principal body systems that are relevant to the studies in this thesis; i.e. aerobic, anaerobic, cardiovascular and respiratory systems.

2-6.1 Aerobic Physiology

Oxygen Uptake

Maximal

The metabolic requirements of exercise increase immediately upon the initiation of physical activity (Sawka, 1986) and $\dot{V}O_2$ is necessarily increased to satisfy the elevated demand. Most of the differences in absolute $\dot{V}O_2$ between maximal UBE and LBE can be attributed to the differences in active skeletal muscle mass, which is assumed to be greater in the latter. Gleser, Hortsman & Mello, (1973) found that $\dot{V}O_{2peak}$ during arm-cranking increased by ~10% when combined with extraneous contractions of the lower limbs, and this was likely to be exacerbated with the gradual inclusion of greater volumes of muscle mass. Oxidative enzyme capacity is also lower (and glycolytic enzyme capacity is higher) in the upper-body (Maughan *et al.,* 1997). Zhang *et al.* (2010) compared changes in muscle oxygenation between the biceps brachi and vastus lateralis during rowing and found that the breaking point (the accelerated fall in muscle oxygenation) and the levelling-off point (the upper-limit of O_2 extraction) occurred earlier in the biceps muscle. This suggested that during rowing, the arms exhibit a lower oxidative capacity compared to the legs. Due to a lower active muscle mass, combined with a lower oxidative capacity, arms-only exercise is considered to be insufficient to induce a maximal stress on the cardiorespiratory systems of healthy, untrained, able-bodied participants (Vokac *et al.,* 1975; Bergh *et al.,* 1976; Cerretelli *et al.,* 1977; Seals and Mullin, 1982; Sawka *et al.,* 1982; Martin *et al.,* 1991; Alison *et al.,* 1998).

Bergh *et al.* (1976) used a multi-mode exercise model to assess indices of oxygen uptake in 10 untrained men. They found that oxygen uptake was largely dependent on the volume of active muscle mass recruited for exercise. These authors also stated that the potential of the organism to use oxygen during exercise was greatest when arm and leg exercise were combined, compared to either pairs of extremities used in isolation. A smaller volume of active muscle mass involved in UBE, combined with a lower maximal power output during arm-cranking (Vokac *et al.,* 1975; Sawka *et al.,* 1982; Louhevaara *et al.,* 1990; Martin *et al.,* 1991), results in peak values for O_2 uptake that are typically ~35% lower during seated arm-cranking than cycling (Stenberg *et al.,* 1967; Miles *et al.,* 1989). Standing arm-cranking results in values for $\dot{V}O_{2peak}$ that are only ~22% lower than cycling (Louhevaara *et al.,* 1990), perhaps due to greater isometric lower-limb activation while standing. Furthermore, maximal arm-cranking induces lower values for cardiac frequency (-11%) and ventilation (-40%) compared to maximal cycling (Martin *et al.,* 1991). Interestingly, participants trained in UBE (i.e. kayakers) can achieve values for arm-crank $\dot{V}O_{2peak}$ that are substantially closer (~90%) to their cycle exercise $\dot{V}O_{2peak}$ (Cerretelli *et al.,* 1977; Seals

and Mullin, 1982). Since the peak aerobic values achieved by trained participants are still considered 'submaximal', it is likely that peripheral muscular factors are responsible for the lower absolute $\dot{V}O_2$ achieved during maximal UBE, and that training-induced adaptations are largely peripheral in nature.

Submaximal

When compared at a given submaximal power output, a majority of studies report higher values for $\dot{V}O_2$ and cardiac frequency during arm-cranking when compared to cycling (Bobbert, 1960; Bevegaard *et al.,* 1966; Stenberg *et al.,* 1967; Vrijens *et al.,* 1975; Toner *et al.,* 1983). This is likely related to a lower gross and net mechanical efficiency for arm-cranking (Eston and Brodie, 1986), and is related to a higher O_2 cost for a smaller absolute volume of muscle mass. The principal mechanisms that elevate O_2 beyond that expected for the smaller active mass during arm-cranking are the increased requirements for muscular stabilisation of the torso (Davies and Sargeant, 1974; Toner *et al.,* 1983), an increased isometric exercise component (Sawka *et al.,* 1982; Bevegaard *et al.,* 1966) and differences in muscle recruitment patterns (Sawka *et al.,* 1982).

In addition to the magnitude of the $\dot{V}O_2$ response, there are substantial differences in the mode-specific O_2-on responses to UBE and LBE. Studies assessing $\dot{V}O_2$ kinetics are concerned with quantifying the time delay that occurs at exercise onset, when deoxygenated blood travels from the exercising limb to the lungs, and pulmonary $\dot{V}O_2$ rises exponentially to satisfy the increases in muscular demand (Koppo *et al.,* 2002). The $\dot{V}O_2$ response to exercise can be subdivided into fast and slow components. The fast component ($\dot{V}O_{2FC}$) results from physical activity of a moderate intensity, i.e. below the gas exchange threshold (GET), in which $\dot{V}O_2$ increases exponentially from baseline and reaches steady-state in ~2 - 3 min (Whipp and Wasserman, 1972; Xu and Rhodes, 1999). This is, of course, dependent on exercise mode and training status. The slow component ($\dot{V}O_{2SC}$) results from heavy exercise, i.e. that performed above the gas exchange threshold, and at this intensity, the $\dot{V}O_2$ steady-state is delayed or may not occur (Whipp, 1994). The $\dot{V}O_2$ time constant for the start of leg exercise is approximately 15 – 30 s (Koppo *et al.,* 2002), but there are numerous reports that the O_2-on response is longer (slower) for arm-cranking (Koppo *et al.,* 2002; Cerretelli *et al.,* 1977; Casaburi *et al.,* 1992; Koga *et al.,* 2001). Furthermore, oxygen uptake kinetics appear to be slower during arm-cranking when compared to cycling performed at the same $\dot{V}O_2$ (Cerretelli *et al.,* 1977) and relative work rate (Schneider *et al.,* 2002).

Differences in the O_2-on response between UBE and LBE may be explained by several mechanisms, including the volume of operating muscle mass, muscle fibre recruitment patterns, blood lactate production, plasma adrenaline concentration, ventilatory and cardiac work and the Q_{10} effect which is associated with increased peripheral and core temperatures (Whipp, 1994; Poole *et al.*, 1992). The predominating hypothesis, however, is the higher O_2 cost and longer time constant of fast-twitch relative to slow-twitch fibres (Crow and Kushmerick, 1982, Kushmerick *et al.*, 1992), which are recruited to a greater extent during UBE.

Fast twitch fibres also have a reduced O_2 utilisation adjustment in response to a standardised muscle contraction than slow twitch fibres (Kushmerick and Crow, 1982). This suggests that upper-body O_2-on kinetics may be limited by the ability of the muscles to utilise O_2 rather than the cardiovascular system to supply it. Moreover, Cerretelli *et al.* (1977) found that the O_2-on response was reduced (faster) following UBE training, and it was speculated that peripheral factors, such as alterations in capillary to fibre exchange surface area, enzymatic oxidative capacity and fibre recruitment patterns, were responsible for the adaptations in O_2 on-response times (Cerretelli *et al.*, 1977). Collectively, these data suggest that peripheral (muscular) factors are largely responsible for slower O_2-on kinetics during UBE compared to LBE. It is for this reason that the O_2 kinetics of trained participants are faster than untrained participants (Fukuoka, Endo, Kagawa, Itoh & Nakanishi, 2002; McNarry, Welsman & Jones, 2012). Since untrained participants were recruited for participation in the experiments of this thesis, it was anticipated that UBE would result in a slower O_2-on response when compared to LBE at a given work rate.

Mechanical Efficiency

The study of mechanical efficiency may provide useful information regarding the energy required to achieve a given amount of external work. In the context of a competitive athlete or a patient in a clinical setting, efficiency provides insight into functional capacity (Smith, Doherty & Price, 2006). When reported in gross or net terms, exercise efficiency tends to increase in line with power output during cycling (Gaesser & Brooks, 1975; Stuart, Howley, Gladden & Cox, 1981; Chavarren & Calbet, 1999) and arm-cranking (Kang *et al.*, 1997; Kang, Chaloupka, Mastrangelo, & Angelucci, 1999; Powers, Beadle & Mangum, 1984). Studies generally agree, however, that UBE results in greater O_2 uptake than LBE at a given submaximal power. Since metabolic efficiency reflects a ratio of work output to aerobic metabolic input, values for UBE gross and net efficiency are accordingly lower as a result (Asmussen and Hemmingsen, 1958; Bobbert, 1960; Astrand and Saltin, 1961; Powers *et al.*, 1984; Kang *et al.*, 1997). The peak mechanical efficiency (power/total energy rate) of fast and slow-twitch fibres are reportedly similar (Barclay, Constable

& Gibbs, 1993), and as such, the disparity in mechanical efficiency is likely due to differences in the absolute volume of muscle recruited.

Particularly pertinent to this thesis, is that values of mechanical efficiency during weight-supported ergometry do not include work performed by internal organs, extraneous limb movements, torso stabilisation or isometric muscular contractions during exercise (Whipp and Wasserman, 1969; Gaesser and Brooks, 1975), and any one of these factors may contribute substantially to the overall energy cost of exercise. Glaser *et al.* (1984) suggested that there may be several unmeasured work components that might alter the magnitude of the O_2 response during UBE, including skeletal muscle activity, transfer of force from skeletal muscle to ergometer propulsion system, isometric exercise and internal work above resting function. An increase in any one of these factors during UBE may elevate $\dot{V}O_2$ and reduce mechanical efficiency.

Finally, contractile-coupling efficiency varies with skeletal muscle fibre type, i.e. compared to slow-twitch muscle fibres, fast-twitch fibres have a lower contractile coupling efficiency (Gibbs and Gibson, 1972). The result is a greater energy cost of performing standardised muscular contractions (Sawka *et al.*, 1971). Since there is a greater fast-twitch fibre distribution in the upper-body (Susheela and Walton, 1969, Gollnick *et al.*, 1972, Johnson *et al.*, 1973), UBE likely impacts unfavourable on the absolute rate of contractile-coupling. This further reduces mechanical efficiency during UBE.

Mechanical Efficiency: a Comparison of Exercise Mode

Chapter 4 of this thesis makes a comparison of arm-cranking to leg-cycling. Both modes are repetitive and cyclical in nature, with similar extremity locomotor mechanical characteristics. Furthermore, neither exercise requires any sports-specific technical coaching. Principally, these exercise modes were selected because the ergometry types are comparable, in that both are related to the amount of mechanical work performed per unit of time (obtained via calculation or calibration of the ergometer; Bobbert, 1959). Exercise research, however, frequently makes physiological comparisons between exercise modes that are not comparable by way of their substantially different locomotor mechanics, e.g. cycling versus running (see Millet, Vleck & Bentley, 2009, for review). Mechanical work can be quantified using characteristics specifically associated with the ergometer, e.g. turning of the flywheel (of a known diameter) at a prescribed rate, against a pre-determined breaking force. During treadmill exercise, however, the speed and gradient of the slope can be determined, but it is only when *walking* on a slope that the physical work per unit of time can be assessed. Bobbert (1959) studied and compared mechanical

efficiency in cycling, arm-cranking and walking and found that the rise in energy expenditure during the two former modes increased linearly with work rate when expressed as increments of absolute power. By contrast, treadmill walkers exhibited a non-linear increase in energy expenditure with increments of either speed or gradient. Furthermore, although arm-cranking and cycling yield differences in *gross* efficiency when compared at absolute work rates, the regression gradients suggest an *absolute* efficiency of 22.1 and 20.3%, respectively, which are closely comparable. There may be less external validity in studies that make physiological comparisons between exercise modes not comparable in terms of absolute efficiency.

2-6.2 Anaerobic Physiology

Blood lactate is used as an indirect marker of anaerobic metabolism. Lactate is produced in response to energy metabolism and is an important energy source that is recycled by intracellular lactate shuttles (Brooks *et al.,* 2000; 2002). Blood lactate production does not influence metabolic acidosis during periods of increased glycolytic flux, but rather it is the ATP supplied from non-mitochondrial sources that increases proton release and induces metabolic acidosis (Robergs *et al.,* 2004). Under such cellular conditions, lactate production increases to prevent pyruvate accumulation and to supply the NAD^+ required for the second phase of the glycolysis reaction. As a result, increased lactate concentrations in the blood coincide with cellular acidosis. Because blood lactate remains a strong indirect marker for cell metabolic conditions that induce metabolic acidosis, many studies report blood lactate concentrations as a marker of anaerobic metabolism.

There are several reports that maximal arm-cranking elicits lower blood lactate concentrations compared to maximal leg-cycling (Secher *et al.,* 1974; Vokac *et al.,* 1975; Sawka *et al.,* 1982). When compared at a given submaximal power or $\dot{V}O_2$, however, it is arm-cranking that results in greater venous blood lactate concentrations (Bevegaard *et al.,* 1966; Stenberg *et al.,* 1967; Sawka *et al.,* 1982; Pimental *et al.,* 1984). This suggests greater anaerobic metabolism during UBE at a given submaximal exercise intensity. These responses are likely associated with the relative intensities of the exercise (Gollnick *et al.,* 1973), i.e. at a given work rate or $\dot{V}O_2$, individuals exercise at a higher percentage of their arm-crank maximal capacity in order to overcome the inertia of the flywheel, than they would during leg-cycling. Indeed, when compared at a range of prolonged, submaximal *relative* intensities, blood lactate concentrations during arm-cranking and leg-cycling are similar (Sawka *et al.,* 1982; Pimental *et al.,* 1984).

The mechanism that underpins the lower blood lactate concentrations during maximal UBE is the lower absolute volume of muscle mass recruited. At a given submaximal work rate, the higher

blood lactate concentrations observed during UBE may be due to several interrelated mechanisms. Principally, the arms have a greater proportion of aerobically meagre type-II fibres when compared to the legs in the same participants (Johnson *et al.*, 1973, Turner *et al.*, 1997), which results in a lower oxidative and greater glycolytic enzyme capacity (Maughan *et al.*, 1997). However, similar *absolute* increases in blood lactate concentration seem to occur following constant-power arm-cranking and leg-cycling (Schneider *et al.*, 2002). Since the volume of active muscle mass is smaller during arm-cranking, it was proposed that the *absolute rate* of lactate production per unit of muscle must be greater in the upper-body (Schneider *et al.*, 2002). There is empirical evidence that the arm muscles release more lactate per unit of active muscle mass than leg muscles, and that a predominance of this lactate is derived from intramuscular glycolysis (Ahlborg and Jensen-Urstad, 1991). Furthermore, the fast-twitch fibres of rat muscles have a greater propensity for Monocarboxylate Transporter 4 (MCT4), which is responsible for the extrusion of lactic acid out of the muscle cells and into the blood where it is measured (Kobayashi, 2004). By contrast, MCT1 is responsible for the transport of lactic acid into the muscle cell, and is of greater concentration in more oxidative fibres. This results in a greater capacity of fast-twitch fibres to shuttle lactate from the muscle and into the blood. Collectively, these data suggest there may be several key mechanisms that underpin the higher blood lactate concentrations of UBE compared to LBE at a given submaximal work rate.

Finally, a review of thirty-two studies reports a strong linear correlation between lactate threshold and endurance performance (Faude, Kindermann & Meyer, 2009). For this reason, many researchers use the aerobic to anaerobic transition during arm-cranking and leg-cycling as a basis for individually evaluating the mode-specific aerobic efficiency. A majority of studies report that during arm-cranking, any given metabolic threshold will occur at a significantly lower percentage of the mode-specific $\dot{V}O_{2peak}$ when compared to leg-cycling. In predominantly untrained participants exercising in both modalities, the anaerobic threshold was reported to occur at 47% $\dot{V}O_{2peak}$ (arm-cranking) versus 54% $\dot{V}O_{2peak}$ (leg-cycling) (Davis *et al.*, 1976). Others report similar trends but higher values of 65% versus 70% $\dot{V}O_{2peak}$ (Reybrouck, Heigenhauser and Faulkner, 1975). Moreover, the lower anaerobic thresholds associated with UBE, combined with higher values for $\dot{V}CO_2$ and $\dot{V}_E$ at a given $\dot{V}O_2$, suggest greater anaerobiosis during UBE compared to LBE (Martin *et al.*, 1991). Collectively, these differences are likely attributable to the lower oxidative capacity of the upper-body musculature. At any given work rate, therefore, anaerobic metabolism is likely to play a greater role in ATP production during UBE. This is an important observation that should be carefully considered when designing upper-body assessment

protocols or training/rehabilitation programmes, particularly for those with cardiorespiratory disease.

2-6.3 Cardiovascular Physiology

Cardiac Output

Cardiac output ($\dot{Q}$) is considered the primary rate-limiting step in maximal aerobic capacity (Bassett and Howley, 2000). $\dot{Q}$ increases during exercise to provide adequate perfusion for O_2 delivery, and remove metabolic by-products (Smith *et al.,* 1976; Rowell & Sheriff, 1988). The magnitude of the $\dot{Q}$ response is closely linked to metabolic function, and during exercise the changes in osmolality, hypoxia and the accumulation of K^+, H^+ and blood lactate metabolites result in a localised vasodilation in the active tissue (Skinner and Powell, 1967). Furthermore, local control of vasodilation is prioritised over the constrictor effects of sympathetic drive (Skinner and Powell, 1967). As a result, the greater the metabolic demand induced by a given exercise, the higher the concentration of anaerobic metabolites and the greater the blood flow response. One would expect, therefore, that exercise performed with a greater volume of active muscle mass would increase $\dot{Q}$ to a greater extent, and indeed, during maximal exercise, $\dot{Q}$ is typically 20 - 30% higher during cycling than seated arm-cranking (Stenberg *et al.,* 1967; Reybrouck *et al.,* 1975). The difference is associated with the disparity in $\dot{V}O_{2peak}$ between the two exercise modes. At a given submaximal $\dot{V}O_2$, however, the available data on the cardiac output response between arm-cranking and cycling suggest that the response is similar (Davies and Sargeant, 1974; Reybrouck *et al.,* 1975; Miles *et al.,* 1984).

What may be particularly important, however, is that the haemodynamics underpinning the $\dot{Q}$ response in UBE and LBE are very different. While stroke volume during cycling increases by approximately 40 - 60% before reaching a plateau (Clausen, 1976; Miles *et al.,* 1984), the stroke volume responses are lower for arm-cranking at any given submaximal $\dot{V}O_2$ (Stenberg *et al.,* 1967; Davies *et al.,* 1974) and either increases slightly or not at all (Clausen, 1976; Clausen & Trap-Jensen, 1976; Franklin, 1985). $\dot{Q}$ during arm-cranking is, therefore, maintained via increases f_C. Individuals with spinal cord injury exhibiting intact cardiac sympathetic drive (paraplegia) also achieve $\dot{Q}$ during exercise predominantly via increases in f_C, whereas those with no sympathetic innervation to the heart (tetraplegia) achieve increases in $\dot{Q}$ via increases in stroke volume (Dela *et al.,* 2003). The inability to expand stroke volume during UBE may, therefore, be associated with a relationship between cardiac sympathetic innervation and exercise mode. The specific haemodynamics of UBE may also be related to differences in vascular pressure, discussed below.

Blood Pressure

According to Poiseiulle's equation, $\dot{Q}$ is the quotient of driving pressure (P) divided by resistance to flow (R). Because blood pressure is reportedly higher during arm-cranking compared to cycling at a given $\dot{V}O_2$ (Pendergast, 1989, Toner *et al.*, 1990), this dictates that resistance must also increase in order to maintain $\dot{Q}$ during UBE. This notion is supported by numerous studies reporting higher values for systolic (Miles *et al.,* 1983; Toner, Glickman & McArdle, 1990; Pescatello, Fargo, Leach & Scherzer, 1991) and diastolic blood pressure (Stenberg *et al.,* 1967; Miles *et al.,* 1984) in addition to total peripheral resistance (Stenberg *et al.,* 1967) during arm-cranking. The mechanisms of the elevated blood pressure response during UBE is multifactorial, but may be attributed to the smaller active muscle mass of arm exercise and lower vasculature of the upper-limbs which offer greater resistance to blood flow (Blomqvist *et al.,* 1981). Stenberg *et al.* (1967) suggested that the higher blood pressure response observed with arm work is a direct result of smaller vascular bed dilation during arm exercise compared to other exercise modes at identical levels of $\dot{V}O_2$ and $\dot{Q}$. Another mechanism that may underpin the blood pressure response to UBE is the control of vasoconstrictor tone. UBE results in a comparatively smaller volume of active mass, and as a result, the vascular cross-sectional area is also smaller. Since blood viscosity and vessel radius are the primary factors controlling resistance to blood flow, the smaller vascular cross-section perfused by the same $\dot{Q}$ results in greater resistance. Arm-cranking also results in small increases in haemoconcentration (4 - 6%) compared to cycling at a given $\dot{V}O_2$ (Miles *et al.,* 1983; Pimental *et al.,* 1984), but this alone would be insufficient to elevate blood pressure.

Finally, there may be several other components contributing to blood pressure control during UBE. For example, isometric muscular contractions of the thoracic muscles associated with postural support, and forceful grasping of the crank handles, both contribute to the isometric exercise component (Jackson *et al.,* 1973), resulting in a more severe pressor response. Furthermore, an elevation in blood pressure resulting from isometric contractions is considered to be influenced by skeletal muscle fibre type, with activation of fast-twitch fibres inducing the greatest increase (Petrofsky *et al.,* 1981). A greater relative proportion of fast-twitch fibres in the upper-body would likely exacerbate the pressor response further. It is also possible that mechanical compression of the vasculature is more severe during UBE, since a smaller muscle mass is required to develop greater muscular tension at any given submaximal power output (Sawka, 1986). Collectively, these data suggest that despite similar changes in $\dot{Q}$ during UBE and LBE, the mechanisms by which this may be achieved are vastly different. The greater systolic blood pressure during UBE is associated with greater cardiovascular strain, and the higher systolic

pressure in the ascending aorta likely increases the work output of the myocardium to overcome ejection pressure. As such, exercise involving small muscle groups (including arm cranking) is perhaps contraindicated for patients with cardiovascular dysfunction, unless specificity of training has been considered.

2-7 Respiratory Physiology

The aerobic, anaerobic and cardiovascular differences between UBE and LBE have been comprehensively assessed. There are, however, relatively few reports on respiratory patterns, and even fewer on respiratory mechanics. Those that have assessed respiratory mechanics during UBE have tended to focus on unsupported arm exercise, which differs from repetitive, cyclical ergometry, i.e. arm-cranking, in some key aspects to be highlighted. Furthermore, a plethora of studies have assessed respiratory mechanics during arm-cranking in obstructive lung disease, which may be of limited use in understanding the healthy response. This section provides a brief overview of the available literature pertaining to the respiratory responses to UBE and LBE.

2-7.1 Ventilation and Respiratory Patterns

At exercise onset, energy demand is instantaneously increased and cell respiration is accelerated. While the circulatory system circulates blood gases to and from the alveoli to sustain cellular respiration, the pulmonary system functions to facilitate the exchange of gases into and from the pulmonary circulation (Brooks *et al.*, 2005). The process is controlled by the motor cortex which sends excitatory signals to the medullary respiratory centre to mediate neural drive to the respiratory muscles. In healthy participants, under normal conditions, ventilation increases accordingly and the relationship between neural drive and ventilation is maintained. Due to the greater operating muscle mass associated with LBE, maximal values of pulmonary ventilation are substantially higher when compared to UBE (Vokac *et al.*, 1975; Magel *et al.*, 1978). When compared at a given $\dot{V}O_2$, however, UBE induces higher values of pulmonary ventilation compared to LBE (Bobbert, 1960; Vokac *et al.*, 1975; Strauss *et al.*, 1977; Sawka *et al.*, 1982; Pimental *et al.*, 1984; Takano, 1993). This can be explained, principally, by disparity in mode-specific metabolic demands, i.e. for a given work rate, participants must exercise at a higher percentage of their mode-specific maximal capacity in order to overcome the flywheel inertia.

Sawka *et al.* (1982) performed a regression analysis to determine if the ventilatory responses to upper- and lower-body exercise were indeed related to the relative exercise intensities. They reported that at relative intensities below 80% $\dot{V}O_{2peak}$, $\dot{V}_E$, $\dot{V}_A$, [BLa] and pH were similar

between exercise modes. At relative intensities above 80% $\dot{V}O_{2peak}$, however, all values (with the exception of pH) were greater during cycling (Fig. 2-5).

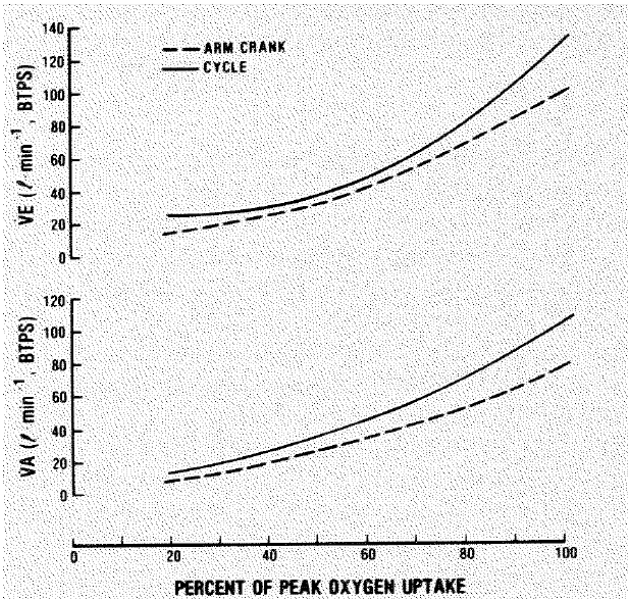

Fig. 2-5: Regression lines of alveolar and pulmonary ventilation from arm-crank and leg-cycle exercise in relation to ergometer-specific relative intensity. (Modified from Sawka *et al.*, 1982).

These data suggest that at submaximal, relative exercise intensities, the responses of ventilation and acid-base equilibrium are similar between UBE and LBE. At work rates approaching maximum, however, the respiratory system is unable to maintain adequate $\dot{V}_E$ and $\dot{V}_A$. This may be associated with the elevated BLa concentrations during maximal cycling which reflect a greater anaerobic metabolite-induced respiratory drive. An alternative consideration, however, is that UBE imposes a mechanical constraint on respiratory function which limits $\dot{V}_E$ at high intensities. This may result from suppressed neural respiratory drive during UBE, or perhaps an exercise-induced dissociation between neural drive and thoracic volume displacement. There is evidence to support this latter hypothesis. Indeed, while $\dot{V}_E$ during LBE is achieved via increases in both V_T and f_R, ventilation during arm exercise is achieved predominantly through increases in f_R (Takano *et al.*, 1993; Alison *et al.*, 1998; Cerny and Ucer, 2004; Hannink *et al.*, 2010). The principal mechanisms that underpin the differences in respiratory pattern are unclear, and further work is needed.

2-7.2 Respiratory Mechanics

Obstructive Lung Disease

Individuals with COPD exhibit reductions in the available inspiratory capacity (i.e. increased EELV) and increased perceptions of dyspnoea during tasks of daily living that involve the arms (Castro *et al.*, 2012). As a result, a majority of the research assessing the respiratory mechanics of arm-cranking have studied those with chronic airflow obstruction (Alison *et al.*, 1998; Porto *et al.*, 2009; Hannink *et al.*, 2010; Castro, Porto, Feltrim & Jardim, 2013). These populations increase their operating lung volumes during exercise in order to avoid expiratory flow limitation (EFL) which may result from a partial collapse of the airway under high expiratory pressures. An increase in exercise EELV above resting (dynamic hyperinflation), decreases airway resistance and increases elastic recoil to aid expiration (Alison *et al.*, 1998; Porto *et al.*, 2009; Hannink *et al.*, 2010). Dynamic hyperinflation is, therefore, a compensatory mechanism initiated to alleviate limitations to expiratory flow. Participants with airway obstruction have a specific pathology that may explain their respiratory responses to exercise. Those with COPD, for example, present with respiratory bronchiole thickening and excess mucous production on the gas exchange surface of the lung due to tissue repair and remodelling processes (Hogg and Timens, 2009) causing limitations to expiratory flow. Moreover, emphysematous destruction of the gas exchanging tissue reduces the elastic recoil pressure available in helping generate expiratory airflow during forced expiration, such as those necessary for expiration during exercise (Hogg, 2008). Due to the lack of studies assessing respiratory mechanics during arm-cranking in healthy participants, it is difficult to discern if the respiratory responses of those with respiratory disease are due to disease pathology or the locomotor mechanics of UBE. Studies in disease populations may, therefore, be of limited use in the understanding those of healthy participants.

Unsupported Arm Exercise

Despite the paucity of literature on arm-cranking, per se, there are several published studies that have assessed respiratory pressures and breathing patterns in healthy participants performing unsupported arm exercise (UAE). During UAE, participants are required to replicate the movements associated with tasks of daily living, e.g. elevating weighted objects above the head (Couser, Martinez and Celli, 1992; Mackey, Ellis and Nicholls, 1998). These studies may provide insight into the functions of the respiratory muscles and ribcage kinematics during UBE. Celli *et al.* (1985) compared UAE to leg-cycling to test the hypothesis that the former would require a greater contribution of the inspiratory ribcage muscles to upper-torso and arm positioning, and thereby decreasing the contribution of these muscles to ventilation. Despite UAE resulting in a lower end-exercise $\dot{V}O_2$, participants exhibited positive pleural-gastric pressure slopes and less

negative end-inspiratory pleural pressure. When matched for V_T, there was a rightward and downward displacement of the slopes. It was concluded that UAE induced a lower ventilatory contribution of the inspiratory muscles of the ribcage due to participation of these muscles in non-ventilatory functions.

Furthermore, Couser *et al.* (1992) determined the respiratory consequences of arm elevation during quiet breathing. When the arms were raised there were increases in $\dot{V}O_2$, $\dot{V}CO_2$, f_C, $\dot{V}_E$, V_T, Poe, Pga and Pdi. After the arms were returned to the resting position, the cardiorespiratory responses remained elevated for ~2 min, whereas intra-thoracic pressures dropped abruptly. Their study suggests that there is a change in respiratory muscle recruitment that is independent of metabolic drive and ventilatory demand. Collectively, these studies support the notion that movements of the upper-limbs may elevate neural respiratory drive in a manner that is unrelated to $\dot{V}_E$. Furthermore, UAE likely increases intra-thoracic pressures by increasing the static, isometric demands on the muscles of the thoracic cage. In healthy participants, this may negatively impact on respiratory mechanics and exercise tolerance. There is a paucity of studies testing these hypotheses, however, and virtually none assessing the responses to dynamic UBE during which the thoracic muscles are involved more vigorously in locomotor and postural activities.

Arm-Cranking

Ventilation during LBE is achieved through the progressive recruitment of abdominal muscles to reduce EELV below relaxation volume (Sharratt *et al.,* 1987; Henke *et al.,* 1988; Grimby *et al.,* 1976; McClaran *et al,*. 1995) resulting in the expansion of V_T. The reduction in EELV may aid inspiration by optimising diaphragm length (Grimby *et al*., 1976, Grassino *et al*., 1981, Henke *et al*., 1988) and is, therefore, mechanically advantageous. When matched for $\dot{V}_E$, however, healthy subjects exhibit an inability to effectively reduce EELV (Alison *et al.,* 1998). Although this response is frequently observed in subjects with chronic airflow limitation due to impending EFL (Alison *et al.*, 1998; Porto *et al.*, 2009; Hannink *et al.*, 2010; Castro, Porto, Feltrim & Jardim, 2013), Alison *et al.* (1998) observed no exercise EFL in their healthy cohort. Furthermore, athletes with cervical spinal cord injury exhibit dynamic increases in both EELV and EILV during constant-power arm-cranking, despite substantial expiratory reserve (Taylor *et al.,* 2010). It is unclear, therefore, if dynamic hyperinflation is typical of UBE, or just specific to UBE performed by those with SCI and/or obstructive lung disease.

An inability to reduce EELV during arm-cranking, as reported by Alison *et al.*, results in a shortening of the inspiratory muscles. In healthy participants, this is mechanically disadvantageous and exacerbates the elastic work of breathing (Milici-Emili and Petit, 1960). This phenomenon may result from a mechanical constraint on V_T, which requires a mechanistic explanation. The inability to control EELV during UBE may have a more complex explanation rooted in the mode-specific locomotor mechanics of UBE during which muscles of the thoracic cage are recruited for postural support, positioning of the arms and stiffening of the spine (Hussain *et al.*, 1985; Celli, 1988; Hodges *et al.*, 2005). The conflicting demands of respiratory muscles may render them less effective at expanding V_T and controlling mechanical ventilation during UBE. Indeed, several authors have implicated the dual roles of thoracic muscles during arm-cranking in the inability to reduce EELV (Alison *et al.*, 1998), compromised breathing capacity (Cerny & Ucer, 2004), elevated cardiorespiratory stress (Price *et al.*, 2007) and increased dyspnoea (Celli *et al.*, 1985). The literature highlighted provides limited insight into the mechanical-ventilatory responses of healthy participants to UBE. Studies assessing intra-thoracic pressures and neural drive to the respiratory muscles during arm-cranking may provide a mechanistic insight.

2-8 The Influence of Cadence Rate on Cardiorespiratory Function

Cadence rates have been shown to influence a number of physiological outcomes during both leg-cycling and arm-cranking, and may provide an effective model with which to further assess the influence of alternating mechanical loads on respiratory responses. To predicate Chapter 5 of this thesis, which quantitatively tests this model, the following is a discussion of the current understanding of cadence influences on cardiorespiratory function.

A majority of cycling studies show an inverse relationship between cadence rate and cycling efficiency; i.e. high cadences result in a reduced cycling efficiency and increased O_2 consumption when compared to low cadences (see Ettema & Loras, 2009, for review). Contemporary studies in arm-cranking also report that high cadences (i.e. 70 - 90 rev·min^{-1}) tend to induce higher values for $\dot{V}O_2$, $\dot{V}_E$, faster O_2-on kinetics and lower values for gross and net efficiency compared to low cadences (50 - 60 rev·min^{-1}; Sawka *et al.*, 1983; Price & Campbell, 1997; Smith, Price & Doherty, 2001; Smith, McCrindle, Doherty, Price & Jones, 2006; Smith, Doherty & Price, 2006; Price, Collins, Smith & Goss-Sampson, 2007).

There are few mechanistic studies that have quantitatively explained these responses, although several suggestions have been put forth. It has been postulated that the elevated cardiorespiratory

stress associated with high crank rates during arm-cranking may be due to greater isometric contractions of the thoracic muscles for torso stabilisation (Price *et al.,* 2007). This is a plausible hypothesis since the rapid and repetitive forces transmitted through the upper-limbs and torso during high cadence arm-cranking likely disrupt the relationship between adjacent spinal vertebrae (Panjabi *et al.*, 1989). This may, in turn, necessitate reactive isometric contractions of various thoracic muscles in order to resist postural disturbances and preserve spinal stability. The hypothesis, however, is insufficient to explain why cardiorespiratory stress is also higher with high cadence cycling, during which the cadence-mediated influence on postural demand is likely to be more modest. An additional explanation, therefore, may be the slower O_2-on response that is reported during low cadence ergometry (Smith *et al.*, 2006). When exercising at low crank rates, a greater muscular tension is required to overcome the increased inertia of the flywheel at any given power. Indeed, the greater forces required at low cadences to produce a given power output result in greater shoulder and trunk ROM (Price *et al.*, 2007) most likely in an effort to recruit greater active muscle mass into the movement. This, in turn, necessitates the recruitment of a greater number of type-II fibres. Since there is a reduced O_2 utilisation adjustment and a longer time constant in type-II fibres compared to type-I fibres (Kushmerick and Crow, 1982; Kushmerick *et al.*, 1992), this would negatively impact on both the O_2-on response and peak aerobic capacity.

A few studies have observed no differences in peak $\dot{V}O_2$, power output, $\dot{V}_E$, f_C or efficiency between high and low cadence arm-cranking (Goosey-Tolfrey, Alfano & Fowler, 2008; Price, Bottoms, Smith & Nicholettos, 2011). However, the null results in these studies may be explained by methodological factors. Price *et al.* (2011) assessed healthy adults while they performed incremental arm-cranking at a constant crank rate (70 rev·min^{-1}) compared to an increasing crank rate (50 rev·min^{-1} for 2 min with 10 rev·min^{-1} increments every 2 min thereafter). The novel protocol is not directly comparable to those used previously in the assessment of cadence on cardiorespiratory function, and the nature of the combined incremental power and cadence protocol may have minimised the difference in absolute physiological responses. Goosey-Tolfrey *et al.* (2008) assessed athletes with spinal cord injury during repeated bouts of arm-cranking at 90 W, performed at either 70 or 85 rev·min^{-1}. The cohort were trained wheelchair athletes competing at international level and, as such, their physiological responses (fibre type distribution, O_2-on kinetics, oxidative capacity, upper-limb and thoracic muscle strength) cannot be compared to untrained populations. Furthermore, spinal cord injuries often lead to disorders in the control of autonomic nerve function, and alterations in the structure and function of sympathetic preganglionic neurons (for review, see Llewellyn-Smith, Weaver & Keast, 2006).

The physiological responses of this population to arm exercise of varying cadence cannot, therefore, be compared to able-bodied participants. Collectively, the available data suggest that crank rates most likely influence physiological function via acute alterations in thoracic muscle loading, and fibre-type recruitment-influences on O_2-on kinetics.

2-8.1 Spontaneously-Chosen Crank Rates

The crank rate spontaneously chosen by healthy, able-bodied people during arm-cranking is reported to be 75 - 80 rev·min^{-1} (Weissland *et al.*, 1997; Dekerle *et al.*, 2002; Smith *et al.*, 2007). Although large inter-individual responses are noted, it is possible that this cadence offers a compromise between the greatest O_2 economy and the least peripheral limb or respiratory discomfort. Interestingly, trained kayakers spontaneously select lower crank rates of ~60 – 70 rev·min^{-1} during incremental arm ergometry (Weissland *et al.*, 1999), and this could be to maximise economy since trained kayakers may be less susceptible to peripheral muscle fatigue. Trained cyclists select cadences of between 83 rev·min^{-1} (Brisswalter *et al.*, 2000) and ~100 rev·min^{-1} (Marsh & Martin, 1993; Marsh & Martin, 1997). Since lower cycling cadences result in the greatest O_2 economy, it is likely that trained cyclists also employ a spontaneously chosen cadence that minimises peripheral muscular fatigue at the expense of mechanical efficiency. There may also exist an 'upper-limit' for a superficially imposed crank rate when non-specifically trained individuals perform arm ergometry at high intensities (> 60% W_{max}), resulting in premature fatigue (Smith *et al.*, 2001). This may be associated with a disruption in the causal relationship between respiratory muscle contraction and pulmonary ventilation that occurs at crank rates ≥ 90 rev·min^{-1}, although this hypothesis remains to be tested.

Chapter 5 of this thesis will assess the influence of cadence on cardiopulmonary function and respiratory mechanics during arm-cranking performed by a group of healthy, but otherwise untrained participants; the study will utilise crank rates of 50, 70 and 90 rev.min^{-1}. Crank rates in the other experimental chapters of this thesis will be standardised at 75 – 80 rev·min^{-1} to reflect the spontaneously-chosen crank rates of untrained people (Weissland *et al.*, 1997; Dekerle *et al.*, 2002; Smith *et al.*, 2007). This cadence is likely to reduce the likelihood of peripheral muscle fatigue while simultaneously maximising mechanical efficiency (Sawka *et al.*, 1983; Price & Campbell, 1997; Smith *et al.*, 2001; Smith *et al.*, 2006a; Smith *et al.*, 2006b; Price *et al.*, 2007).

2-9 Skeletal Muscle Fatigue

Skeletal muscle fatigue is defined as a reduction in force- and/or velocity-generating capacity of a muscle under power and which is relieved with rest (NHLBI Workshop, 1990). Since the force-generating capacity of the respiratory muscles cannot be directly quantified, the pressure change in the respiratory airways is used as a surrogate measure of force output. Centrally, fatigue results from a reduced excitatory input to higher motor centres and/or excitatory drive to lower motoneurons (Bigland-Ritchie, 1984). Some have suggested that a centrally-mediated reduction in neural drive to exercising muscle is pre-emptively initiated to prevent damage to splanchnic regions (Bigland-Ritchie and Woods, 1984). Peripherally, fatigue may occur at several phases. For example, there may be a failure in action potential propagation along the muscle surface membrane (Jones, 1996; Sjogaard, 1996) which affects calcium release from sarcoplasmic reticulum. Such fatigue is considered to occur due to the loss of force output following high frequencies of stimulation (high-frequency fatigue, HFF). There may also be muscular fatigue associated with processes at the distal end of the motor unit, i.e. impaired excitation-contraction coupling (Laroche *et al.*, 1989) and/or damaged fibre sarcomeres due to overextension of the muscle during concentric and eccentric contraction (Jones, 1996). Such fatigue results in the loss of force output following low frequencies of stimulation (low frequency fatigue, LFF). This section begins with a brief summary of the current understanding of central and peripheral fatigue. A discussion on the various techniques used to assess fatigue of the respiratory muscles is then presented.

2-9.1 Central Fatigue

Central fatigue has been described as a reduced excitatory input to higher motor centres and/or excitatory drive to lower motoneurons (Bigland-Ritchie, 1984). Fatigue attributable to suboptimal output from the central nervous system results in the inability of a participant to achieve total muscle activation despite attempting to initiate a maximal voluntary contraction. In this instance, the tension achieved would be below that generated by supramaximal high-frequency (50 – 100 Hz) tetanic electrical stimulation (Merton, 1954). Central fatigue may result from several factors including reflex inhibition and disfacilitation, Renshaw cell inhibition, and insufficient drive from supraspinal sites (Gandevia, 1998). A common technique for the assessment of central fatigue is to superimpose an electrical or magnetic stimulus on a voluntary effort, known as twitch interpolation. Under such conditions, if voluntary activation is submaximal, the external stimulus augments neuromuscular activation and increases force or pressure generation (Laroche *et al.*, 1989). Central fatigue has been observed in studies of the human diaphragm. In a milestone study by Bellemare & Bigland-Ritchie, (1987) the phrenic nerves were stimulated following

resistive inspiratory loading to exhaustion. When participants were unable to achieve the target Pdi during inspiration (suggestive of diaphragm fatigue), twitch interpolation produced a considerable $P_{di,tw}$. The authors concluded that under the conditions investigated, approximately 50% of diaphragm fatigue was central in origin.

2-9.2 Peripheral Fatigue

High Frequency Fatigue (HFF)

High frequency fatigue is characterised by an excessive loss in pressure/force generation of a muscle in response to high frequency stimulation (50 – 100 Hz) that recovers rapidly (Jones, 1996). This form of fatigue is due to a failure of excitatory processes at the neuromuscular junction and muscle cell membrane (Laroche *et al.,* 1989). HFF is most likely associated with potassium ion (K^+) release from active muscle cells that then accumulates in the inter-fibre spaces of the muscle. This, in turn, prevents the propagation of action potentials along the surface membrane (Sjogaard, 1996). HFF can, therefore, be assessed via EMG which will exhibit a rapid reduction in excitatory amplitude (Laroche *et al.,* 1989). High motor neurone firing frequencies can be achieved during voluntary contractions, generating force that is equivalent to that achieved with high frequency electrical stimulation (Merton, 1954). The decline in force output, however, is less than that induced with a 100 Hz stimulation, and is generally observed in the context of fatiguing laboratory studies. When the respiratory muscle pump is sufficiently loaded, the CNS may reduce central drive sufficiently to avoid HFF (Laroche *et al.,* 1989). HFF is not considered, therefore, to occur in the clinical setting (Merton, Hill and Morton, 1981).

Low Frequency Fatigue (LFF)

Low frequency fatigue is characterised by reduced muscular tension resulting from low frequency stimulation (Fig. 2-6). LFF can be measured via electric or magnetic twitches delivered to the peripheral nerves innervating the muscles (Edwards *et al.,* 1977). During LFF, muscle contractility may remain depressed for hours or days following high-intensity exercise (Jones, 1996), despite *normal* neuromuscular and muscle membrane function. LFF likely results from a combination of two interrelated mechanisms. First, there may be a reduction in the action potential-induced secretion of Ca^{2+} release from SR (Jones, 1996). This will affect thick and thin filament cross-bridge cycling and reduce the strength of muscle contraction. In direct measurements of intracellular Ca^{2+} in mammalian muscle fibres, Westerblad *et al.* (1993) showed a consistent reduction in intracellular Ca^{2+} concentration in fatigued fibres. Some authors suggest that LFF may also result from a reduced sensitivity of troponin for Ca^{2+}, however, Westerblad *et al.* observed no alteration in either intracellular buffering of Ca^{2+}, or in the relationship between

tension and intracellular Ca^{2+}. This suggests that LFF is primarily the result of reduced Ca^{2+} availability and not reduced troponin sensitivity. LFF may also result from structural damage to the sarcomeres caused by prolonged, forceful contractions of the active muscles which negatively impacts on the excitation-contraction mechanism (Jones, 1981). This may be particularly common in muscles that fatigue as a result of excessive stretch or prolonged isometric contractions while extended (Jones, 1996). Such structural damage likely results from stretching of the sarcomeres at the end of the fibre which, in turn, damages the weaker middle section causing it to become elongated (Morgan, 1990). As a result of 'popping sarcomeres', the centrally damaged portion of the muscle fibre results in a reduction in pressure and/or force production that is independent of changes in Ca^{2+} concentrations. LFF that takes days to recover is thought to result from sarcomere damage, whereas recovery taking only hours is more likely associated with intracellular Ca^{2+} availability. Contractile fatigue of the respiratory muscles is likely to be that of a low frequency.

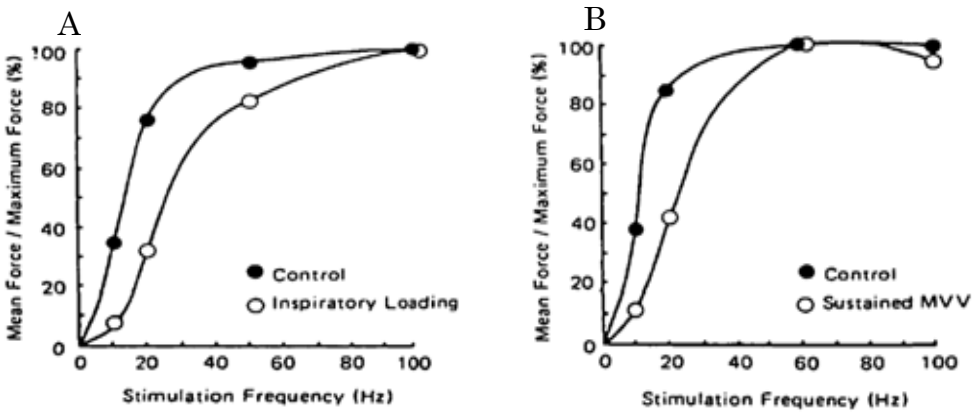

Fig. 2-6: Low frequency fatigue of the sternomastoid muscle after two fatiguing respiratory manoeuvres. Inspiratory loading (panel A) and sustained maximal voluntary ventilation (panel B). (Moxham, Wiles, Newham, Edwards, 1980).

2-9.3 Assessment of Respiratory Muscle Fatigue

Skeletal muscles, including the respiratory muscles, have two primary functions: to develop force and to shorten. Assessing the effectiveness with which skeletal muscles perform these functions can be used as a means to evaluate and quantify peripheral fatigue. Due to the relative difficulty in accessing the deep respiratory muscles, i.e. diaphragm, using conventional methods, pressure and volume changes with time are usually measured as a surrogate for force production (American Thoracic Society/European Respiratory Society, 2002).

Despite the complex processes and underlying mechanisms of respiratory muscle fatigue, diagnostic measures are essential to ensure the appropriate detection in the research setting, in addition to providing optimal treatment in pulmonary rehabilitation and sports medicine. A variety of methods have been used in the assessment of respiratory muscle fatigue; these include the monitoring of respiratory patterns (V_T and f_R), thoracoabdominal motions, pressure-time index (PTI), maximal volitional pressure manoeuvres and muscle responses to external stimuli (ATS/ERS Tests of Respiratory Muscle Strength, 2002). There is no consensus on the optimal protocol for detection. Furthermore, a full discussion of each method and the potential advantages and disadvantages is beyond the scope of this review. A recent systematic review of studies assessing inspiratory muscle fatigue, however, analysed 84 studies across the literature and summarised that when assessing inspiratory muscle fatigue, 44% of studies used maximal voluntary pressure manoeuvres and 64% used nerve stimulation techniques (Janssens, Brumagne, McConnell, Raymaekers, Goossens *et al.,* 2013). The following section, therefore, outlines the two most pertinent assessment strategies used in the identification of respiratory muscle fatigue in healthy humans.

2-9.4 Maximal (Volitional) Respiratory Muscle Pressure

Measuring the maximum static inspiratory (P_{IMAX}) or expiratory (P_{EMAX}) pressure that a participant can generate at the mouth is a simple, non-invasive way to gauge inspiratory and expiratory muscle strength. Similar manoeuvres may be used to assess changes in Pdi, Poe and Pga. The pressure measured during a given manoeuvre is indicative of the pressure developed by the respiratory muscles. Moreover, the peak value represents both the pressure developed by the respiratory muscles, and the passive elastic recoil pressure of the respiratory system including the lung and chest wall (ATS/ERS Tests of Respiratory Muscle Strength 2002).

Maximal static pressure manoeuvres are commonly performed with a mouth-pressure meter and do not require the placement of invasive and potentially uncomfortable oesophageal catheters.

The participant is required to perform a maximal inspiratory or expiratory effort into a mouthpiece. The mouthpiece contains a small leak (~2 mm diameter) to prevent closure of the glottis during the P_{IMAX} manoeuvre, and to minimise the use of buccal muscles during the P_{EMAX} manoeuvre. Participants are instructed to sit upright during each manoeuvre since posture can substantially impact the values obtained (Ng and Stokes, 1991). Skeletal muscle fatigue is defined as a loss of capacity to develop force (pressure) in response to a load and is reversible with rest (Aldrich, 1988), and as such, fatigue of the respiratory muscles can reasonably be assessed by measuring a reduction in maximal volitional respiratory pressure. Indeed, P_{IMAX} measured at the mouth has been used as a global measure of inspiratory muscle fatigue after breathing against external loads (Aldrich, 1988), maximal voluntary hyperpnoea (Bai, Rabinovitch, Pardy, 1984), endurance exercise (Loke, Mahler, Virgulto, 1982; Chevrolet *et al.*, 1993) and fatiguing bouts of sit-ups (Gomez, Strongoli and Coast, 2009). For a review of the methods most commonly used in assessing inspiratory muscle fatigue, see Janssens *et al.* (2013).

A potential disadvantage of using maximal static pressure manoeuvres in the assessment of respiratory muscle fatigue is that reproducibility is dependent on the participant's ability to give a maximal voluntary effort. In highly-motivated, healthy participants, whom have received adequate training and familiarisation, this may not be a concern. Low results or poor reproducibility may result, however, from a lack of motivation or technical ability. Furthermore, maximal static efforts are usually associated with high firing frequencies and are, therefore, a poor indicator of the LFF that usually causes fatigue of the respiratory muscles following high-intensity exercise (ATS/ERS Tests of Respiratory Muscle Strength, 2002).

A further limitation of these measures in the detection of respiratory muscle fatigue is the lung volume at which the manoeuvre is performed. While P_{IMAX} is usually performed from residual volume, P_{EMAX} is usually performed from total lung capacity. Performing manoeuvres from different lung volumes results in variations in the magnitude of ribcage and abdominal wall elastic recoil. Indeed, when pressure is measured at the mouth, the passive elastic recoil of the respiratory system at TLC and RV can contribute ~40 cmH_2O and 30 cmH_2O, respectively (ATS/ERS, Tests of Respiratory Muscle Strength 2002). It has been suggested, therefore, that maximal volitional mouth pressure manoeuvres be performed from relaxation volume (FRC) where recoil is zero and mouth pressure is representative of respiratory muscle pressure. This too may be problematic, however, since small changes in lung volume, at FRC, are associated with large changes in respiratory pressure, whereas measurements from TLC and RV result in changes in lung volume that have minimal influence on pressure (Fig. 2-7). As a result, any change in

FRC pre- to post-exercise could substantially impact on respiratory muscle pressure output and falsely represent respiratory muscle strength, and subsequent measures of fatigue. For this reason, P_{IMAX} and P_{EMAX} manoeuvres performed in the current thesis will be performed from TLC and RV, respectively.

2-9.5 Artificial (Involuntary) Nerve Stimulation

Nerve stimulation is an objective means by which to assess respiratory muscle contractile fatigue. The technique may involve electrical or magnetic stimulation, allowing specific muscles or groups of muscles to be isolated for assessment. Studies artificially stimulating the expiratory (Chokroverty *et al.,* 1995; Lin *et al.,* 1998; Polkey *et al.,* 1999; Man *et al.,* 2004; Taylor *et al.,* 2006) and inspiratory (Similowski *et al.,* 1989; Johnson *et al.,* 1993; Similowski *et al.,* 1998; Mador *et al.,* 2002; Man *et al.,* 2004) muscles have been documented. The technique involves delivering stimulations to the central (e.g. transcranial magnetic stimulation) or peripheral (e.g. cervical magnetic stimulation) nervous systems. In turn, the pressure response from artificial stimulation is a useful objective measure of respiratory muscle contractility (Suzuki *et al.,* 1999). Electrical stimulation has been used to activate superficial muscles of the abdominal wall (Mier *et al.,* 1985; Suzuki *et al.,* 1999). In Chapter 6 of this thesis, however, we preferred magnetic versus electrical stimulation because the latter is ineffective at stimulating the deeper abdominal muscles that are recruited as ventilation increases (Van Gansbeke and Gorini, 1990; Abe and Kusuhara, 1996). Furthermore, magnetic stimulation does not activate cutaneous pain receptors and is, therefore, well tolerated by participants (Polkey *et al.,* 1999; Taylor *et al.,* 2009). Magnetic stimulation at the neuroforamina is often used in clinical examinations, as well as research, and allows the measurement of the compound muscle action potential (CMAP) latency (Ugawa *et al.,* 1989) as well as amplitude and area.

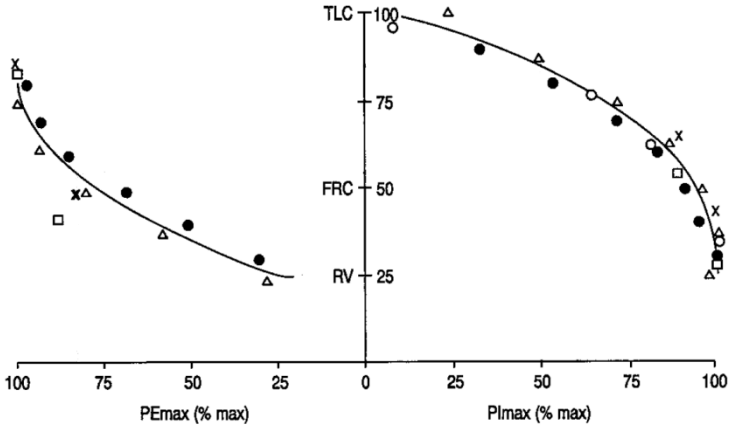

Fig. 2-7: Relationship between maximal static expiratory and inspiratory pressure (P_{IMAX}, P_{EMAX}) and lung volume. Pressures are expressed as a percentage of maximum and the lung volume is expressed as a percentage of TLC (Rochester, 1988).

2-9.6 Assessing Respiratory Muscle Fatigue

By artificially stimulating the peripheral motor nerves, fatigue can be measured from the change in force output relative to baseline values. While measuring force output of the locomotor muscles, e.g. quadriceps, is relatively easy, the deep respiratory muscles are fairly inaccessible. As a result, force output across the muscle is estimated by assessing pressure development in the airway. In the current thesis, transdiaphragmatic pressure was estimated by measuring the pressure difference between gastric and oesophageal pressures induced by stimulation of the phrenic nerve roots (Aubier *et al.,* 1981; Mills *et al.,* 1996; Similowski *et al.,* 1989). Abdominal muscle force output was estimated by measuring the gastric pressure response to magnetic stimulation of the thoracic nerve roots (Kyroussis *et al.,* 1996; Taylor *et al.,* 2006).

A potential disadvantage of using nerve stimulation to assess contractile fatigue of the respiratory muscles is that oesophageal catheters are required to assess changes in gastric and oesophageal pressures following stimulation. Placement of these catheters is invasive, and although considered safe, is not tolerated by all participants. Furthermore, in much the same way as maximal static pressure measures, artificially evoked respiratory muscle pressure responses are influenced by changes in lung volume, i.e. the lung volume assumed by a participant immediately prior to a given stimulation (Polkey *et al.,* 1998; Polkey *et al.,* 1999). While lung volume has a significant effect on the diaphragm pressure response to low-frequency magnetic stimuli, there appears to be only minimal influence of lung volume on gastric pressure (Polkey *et al.,* 1998). In any case, artificial stimuli must be delivered at a known lung volume (usually FRC) and care must be taken to familiarise participants with reaching and maintaining the appropriate lung volume.

2-10 Summary

There are fundamental differences in the cardiorespiratory responses to exercise performed with the upper-body when compared to the lower-body. Although a predominance of these differences may be explained by the difference in active muscle mass between UBE and LBE, there may be several other contributing factors including fibre-type distribution, oxidative capacity and haemodynamics. While some authors have assessed respiratory mechanics in healthy participants performing basic upper-limb tasks, there is a paucity of literature assessing the respiratory mechanics of healthy participants during dynamic locomotor activities. There is evidence to suggest that mechanical-ventilatory efficiency may be negatively influenced by the locomotor mechanics of UBE during which the respiratory muscles may be required for combined ventilatory, postural and locomotor functions. This may, in turn, make the respiratory muscles particularly susceptible to fatigue.

2-11 Thesis Aims

In consideration of the evidence discussed in the preceding literature review, the thesis aims are:

1. To characterise cardiorespiratory responses and respiratory mechanics (intra-thoracic pressures, operating lung volumes, ventilatory constraint, expiratory muscle activity) during upper-body exercise performed by healthy adults.
2. To assess the acute influence of cadence and work rate on cardiorespiratory indices, mechanical-ventilatory responses, diaphragm activity and locomotor-respiratory coupling during submaximal upper-body exercise in healthy adults.
3. To objectively assess whether upper-body exercise is sufficient to induce contractile fatigue of the inspiratory and expiratory muscles, and to investigate the affect of work rate on the incidence and magnitude of fatigue.

Chapter Three

GENERAL METHODS

The current chapter provides a detailed explanation of the methods frequently used in this thesis. The principal items of equipment and techniques applied will be covered, in addition to procedures that are common to the experimental chapters. Methods that relate to specific experimental chapters are outlined in the respective methods sections.

3-1 Ethical Approval and Participant Consent

Ethical approval for each study was received from the School of Sport and Education Research Ethics Committee prior to each study. Since the third experiment subjected volunteers to electromagnetic nerve stimulation, ethical approval was also sought (and received) from the Brunel University Research Ethics Committee (Appendix A). Participants were verbally briefed on all experimental procedures and were given detailed written copies of the study-specific protocols. Each participant was required to complete a health questionnaire (Appendix B). Before providing written informed consent (Appendix B), participants were informed that they could withdraw from the study at any time, without subsequent penalty or prejudice, and where relevant, without it affecting their University grades.

3-2 Participants

Participants from the University student population volunteered to participate in experimental procedures. The exclusion criteria for all three studies were that participants must be healthy males, non-smokers, recreationally active, between the ages of 18-45 yr and free from any acute or chronic cardiovascular or respiratory diseases. Participants were excluded from the study if they were heavily weight-trained or had undergone systematic strength or endurance training in the 4 months prior to data collection. Due to the use of lidnocaine hydrochloride in the positioning of oesophageal catheters, participants were also excluded if they knew that they would have an adverse reaction to anaesthesia or if they were allergic to peanuts, since the latter increases the likelihood of anaesthesia sensitivity. Since latex gloves were used by the researcher throughout experimental procedures, participants were also excluded if they had a pre-existing latex allergy.

3-3 Baseline Pulmonary Function

Pulmonary function was completed prior to data collection. In Chapter 4, pulmonary function was assessed using spirometry. In Chapters 5 and 6, pulmonary function was assessed using spirometry, whole-body plethysmography and CO rebreathe according to recommended standards (Miller *et al.* 2005; Wanger, 2005; Macintyre *et al.* 2005). Prior to formal data collection,

participants were taken through an informal familiarisation session during which all respiratory manoeuvres were demonstrated by the researcher and then practiced by the participant.

3-3.1 Spirometry

In Chapter 4, standard indices of pulmonary function were assessed using an online spirometer (Oxycon Pro, Jaeger GmbH, Hoechberg, Germany). The spirometer incorporated a lightweight impeller attached to a volume transducer which detected the number of completed fan revolutions per second to differentiate for flow. The flow and volume signals were fed through a signal amplifier (1902, Cambridge Electronic Design, Cambridge, England) and digitised at 150 Hz using an analogue-to-digital converter (micro 1401 mkII, Cambridge Electronic Design, Cambridge, England). During respiratory manoeuvres, spontaneous measurements of volume, flow, EMG and intra-thoracic pressures (discussed below) were integrated using data acquisition software (Spike 2 version 7.00, Cambridge Electronic Design, Cambridge, England). This allowed digital waveforms of all responses to a given manoeuvre to be analysed simultaneously (Fig. 3-1). In Chapters 5 and 6, spirometry was assessed using a pneumotachograph (Vmax Vyntus, CareFusion, Hampshire, UK).

Respiratory manoeuvres were made while participants were sat upright on a chair with a back support. The nose was occluded and participants breathed into a flanged mouthpiece (Chapter 4) or a plastic MicroGard Filter (Chapters 5 and 6; CareFusion, Hampshire, UK). They were instructed to make a tight seal around the mouthpiece, but to avoid excessive biting and to ensure the tongue was not occluding airflow. Participants were instructed to inhale rapidly to maximal lung volume and, with < 1 s pause, forcefully 'blast' the air outwards with a maximal exhalation, and continue the manoeuvre until no more air could be moved from the lungs. Once maximal expiration had been achieved (with expiration > 6 s when possible), participants were instructed to maximally inhale to complete the flow-volume loop. The flow-volume profile allowed the determination of FVC, FEV_1 and the FEV_1/FVC ratio.

All maximal flow-volume measurements conformed to specific criteria outlined by the American Thoracic Society/European Respiratory Society (Miller *et al.*, 2005). Briefly these were: 1) at least three reproducible efforts were made, i.e. the two largest values of the sum of FVC and FEV_1 that did not differ by more than 150 ml, but with a maximum of 8 manoeuvres; 2) expiratory effort during the FVC manoeuvre lasted for ≥ 6 s; 3) a plateau occurred in the volume-time curve. Participants were also required to complete two maximal voluntary ventilation (MVV) manoeuvres. Briefly, participants were instructed to perform repeated maximal respiratory efforts

for 12 s into the mouthpiece, in a fashion that replicated the respiratory patterns of maximal exercise. Participants were given verbal cues to begin and end maximal ventilation. Volume and flow measurements recorded during spirometry were expressed as BTPS.

In order to determine the exact lung volumes produced, the spirometer was calibrated prior to each measurement using a 3 L calibration pump (Jaeger Calibration Pump, Jaeger GmbH, Hoechberg, Germany). The pump piston was pulled back and forth with smooth, regular motions, taking care to fully empty and fill the pump with each repetition. The correction factors for inspired and expired volumes were logged on a computerised system and the researcher alerted with an error message if volume deviated from the acceptable range.

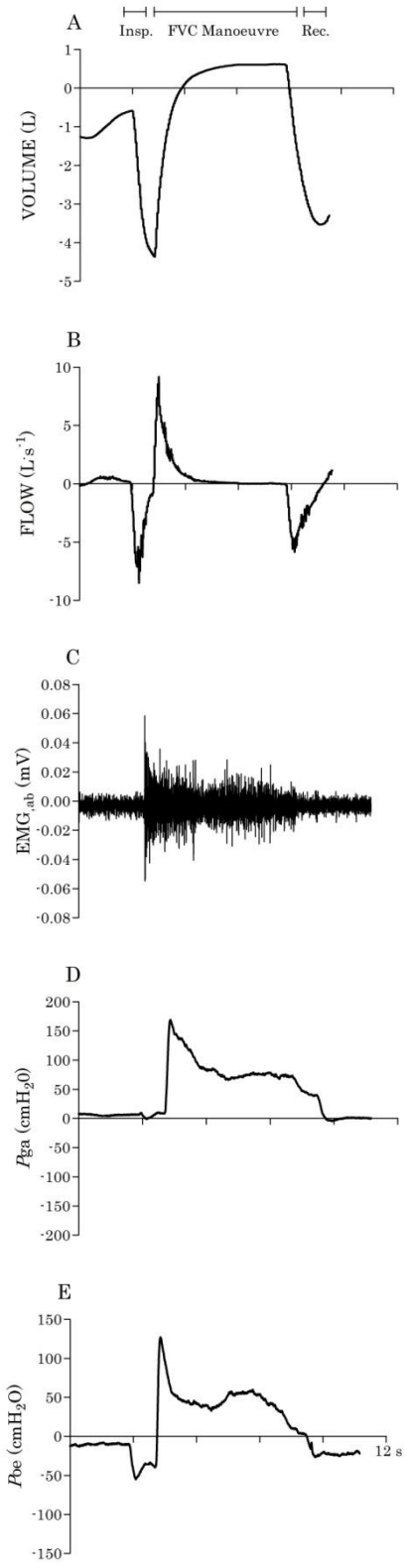

Fig. 3-1: Volume (panel A), flow (panel B), EMG of the rectus abdominis (panel C), gastric pressure (panel D) and oesophageal pressure (panel E) recorded during a forced vital capacity manoeuvre prior to exercise. Integrating signal waveforms allowed the simultaneous analysis of multiple indices of respiratory function. See below for a description of pressure and EMG measurements.

3-3.2 Whole-Body Plethysmography

Prior to experiments in Chapters 5 and 6, lung volumes and airway resistance were measured using a whole-body plethysmograph (Masterscreen, CareFusion). The principle of measurement in body-plethysmography relies on Boyles Law: 'for a fixed amount of gas in a closed compartment the relative changes in the compartment's volume are always equal in magnitude but opposite in sign to the relative changes in pressure' (West, 2005). By detecting changes in box pressure, in combination with either changes in mouth pressure (when breathing through an occluded mouthpiece) or with flow rate under defined breathing conditions, it is possible to infer absolute and relative volume changes (Criee *et al.*, 2011). The whole-body plethysmograph was used to determine static lung volumes and airflow resistance that are not possible with standard spirometry. Participants were required to sit upright in the plethysmograph, with the nose occluded, and instructed to adjust the height and orientation of the mouthpiece (MicroGard Filter, CareFusion). Once comfortable, participants began resting tidal breathing for the assessment of airway resistance (Raw). Airflow during spontaneous breathing was continuously recorded from the pneumotachograph and displayed against the shift in volume produced by thoracic compression and decompression. The measurement of total-airway resistance required two pressure transducers to measure the pressure drop across the airway and a pneumotachograph connected to a differential pressure transducer for the measurement of flow. Following the attainment of acceptable resistance curves, i.e. three signals in phase up to a frequency of 10 Hz (Fig. 3-2), thoracic gas volumes were then assessed.

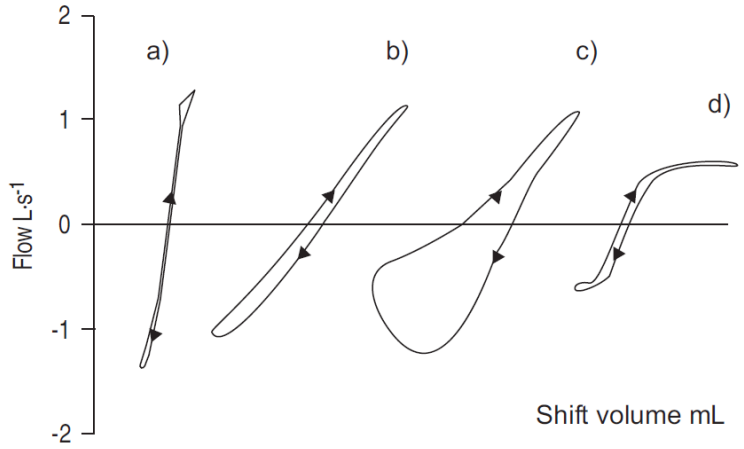

Fig. 3-2: Schematic representation of specific resistance loops in a) a normal participant, b) a participant with increased large airway resistance, c) a participant with chronic airflow obstruction d) and a participant with upper airway obstruction. These curves show the slope used for calculation of total sRaw. Inspiratory and expiratory flows are plotted on the vertical axis. Inspiratory and expiratory shift volume is plotted on the horizontal axis. In both cases, inspiration is positive and expiration is negative (Goldman, Smith & Ulmar, 2005)

Thoracic gas volumes were assessed with the aid of a shutter mechanism, positioned close to the mouth, which was used to provide transient airway occlusion. Participants were forewarned that the shutter would close at the end of the next expiration, and were instructed to continue breathing in a relaxed manner, and to not deviate from their resting breathing frequency or level of respiratory effort. Voluntary respiratory efforts were performed by the participant against the occluded shutter, during which the change in alveolar pressure (P_A) was estimated by recording the change in mouth pressure (P_M). P_M was then plotted against simultaneous plethysmographic pressure changes to measure absolute TGV. The shutter re-opened after 2 – 3 s and the participant performed slow but maximal ERV and IRV manoeuvres for the calculation of static lung volumes.

The pneumotachograph was calibrated for volume using procedures described previously (see *Spirometry*). Prior to use, the plethysmograph pressure transducer was calibrated in terms of changes in thoracic gas volume (TGV). The door was first closed to allow stabilisation of box volume and pressure. This calibration was completed internally (automatically) using a motor-driven syringe. During calibration, 30 – 50 mL air was repeatedly introduced and withdrawn from the box chamber. Post-calibration, changes in pressure reflected changes in TGV due to compression/decompression of thoracic gas. The calibration was then corrected for the participant's body volume, using the participant's body mass to calculate the final adjusted calibration coefficient.

3-3.3 CO Rebreathe

Single-breath CO diffusion capacity (transfer factor, $D_{L,CO}$) was used to estimate the diffusion capacity of the lung for O_2. Following an automatic 'zero adjustment' during which atmospheric air was sampled, participants assumed resting tidal breathing into a mouthpiece with the nose occluded. At the end of a maximal expiration to RV, a fast and maximal inspiration to TLC triggered the release of carbon monoxide gas of a known concentration into the mouthpiece. Maximal inspiration must be completed in <2 by healthy participants, and <4 s by patients (ATS/ERS, 2005). At peak inspiration, participants were required to hold their breath against an open glottis for ~8 – 10 s; the shutter was occluded to prevent premature expiration, and the manoeuvre disregarded if pressure across the mouthpiece exceeded >3 kPa as this would be suggestive of an expiratory effort. After the allotted time, participants were encouraged to slowly but maximally exhale back to RV. The difference in CO concentration between inspired and expired manoeuvres was expressed in $mmol \cdot min^{-1} \cdot kPa^{-1}$. Prior to use, the system was calibrated using a calibration gas cylinder containing Helium (2.5 – 10%) and Carbon Monoxide (0.15 – 0.30%).

3-4 Cardiorespiratory Parameters

3-4.1 Pulmonary Ventilation

Indices of pulmonary ventilation were made on a breath-by-breath basis using a low resistance (< 0.1 $kPa \cdot L \cdot s^{-1}$ at 15 $L \cdot s^{-1}$), high resolution bidirectional digital volume sensor with a volume and flow range of 0-10 L and 0-15 $L \cdot s^{-1}$, respectively. The flat fan design was 45 g and, therefore, had minimal inertia (and thus, resistance to airflow) when compared to a traditional turbine. The volume sensor was interfaced with an online gas analyser (Oxycon Pro, Jaeger GmbH). The sensor was positioned near the mouthpiece where the stream of airflow would cause the impeller to rotate. Each revolution of the impeller interrupted a light beam and the number of interruptions in a given time period was computerised to estimate volume and ventilation. From the airflow signal generated by the transducer, inspired and expired volumes were calculated by integrating the areas below and above the line of zero flow, respectively. Using indices of tidal volume (V_T) and time, other variables including respiratory frequency (f_R) and minute ventilation ($\dot{V}_E$) were calculated. Volume and flow data were passed through a data acquisition system (uDAQ Special, CareFusion) where the analogue ventilatory signals were processed and transmitted instantaneously to an analogue-to-digital converter (micro 1401 mkII, Cambridge Electronic Design) and displayed as waveforms alongside digital traces for pressure and EMG using data analysis software (Spike 2 version 7.00, Cambridge Electronic Design, Cambridge, England). When assessing flow, anomalous breaths were considered to be those exceeding the upper- or lower-limit of 3 standard deviations of the mean, or breaths not crossing the line of zero flow and were excluded from analysis. Before each set of measurements, the fan transducer was calibrated for volume and flow using a 3 L manual calibration pump (Jaeger Calibration Pump, Jaeger GmbH), described previously.

3-4.2 Gas Exchange

In addition to the volume and flow sensors used in assessing pulmonary ventilation, the online system housed a high speed O_2 sensor which was based on a chemical fuel cell and had a range of 0 - 25%. The CO_2 analyser operated on the infrared absorption principle and had a range of 0 - 15%. Both sensors continuously sampled expired air at the mouth using a fine tube catheter. The system as a whole had the following measurement range: $\dot{V}_E$ = 0 - 300 $L \cdot min^{-1}$, $\dot{V}O_2$ = 0 - 7 $L \cdot min^{-1}$, $\dot{V}CO_2$ = 0 - 7 $L \cdot min^{-1}$, RER = 0.6 - 2.0. Given that all the participants were recreationally-active adult males, the system range of measurement was more than suitable for cardiopulmonary exercise testing of this population. The online system came equipped with a function that allowed the automatic interpretation of metabolic thresholds based on the decision tree method (Wasserman, 1984), which was used only in support of the manual calculations of

metabolic thresholds (see below). Prior to every test, the gas analysers were calibrated across the physiological range using a certified gas mixture of 5% CO_2, 15% O_2 and 80% N_2 (BOC Gases, Guilford, UK). The gas analyser used throughout experimental procedures has been positively validated against the Douglas bag method (Rietjens, Kuipers, Kester & Keizer, 2001; Carter & Jeukendrup, 2002).

3-4.3 Gas Exchange Thresholds

Chapters 5 and 6 required participants to exercise at predetermined work rates based on varying percentages of the gas exchange threshold (GET). This metabolic threshold was calculated manually using multiple parallel methods described by Wasserman (1984) and Beaver, Wasserman & Whipp, (1986). What follows is a brief description of these methods including example plots of representative data.

Although exercise work rates are more commonly based around GET, it is useful to calculate both thresholds within a given ventilatory profile so as to minimise the likelihood of misidentifying the GET. The $\dot{V}_E$ and work rate at a given threshold were established from multiple scatter plots based on the cardiorespiratory responses to a maximal ramp incremental exercise test. First, a scatter plot of $\dot{V}_E$ versus $\dot{V}CO_2$ was drawn using 10 s averages and used to establish the respiratory compensation point. The RCP was identified by locating the point at which there was an exponential increase in ventilation triggered by unbuffered H^+ ions (Fig. 3-3, panel A). Even though exercise work rates were not based around the RCP, the initial plot was important to ensure that the RCP was not mistakenly identified as the GET. Second, a scatter plot of $\dot{V}O_2$ versus $\dot{V}CO_2$ was drawn to identify the GET. This was the first metabolic threshold and was caused by the buffering of H^+ ions with carbonic acid producing CO_2 which was additional to naturally expired CO_2. In this plot, the early and late portions, when CO_2 was being loaded into body stores, was ignored. The threshold was found by identifying the work rate at which the data points deflected against the line of identity (Fig. 3-3. panel B). At this stage, confidence for the correct identification of GET was identified as high, medium or low. If confidence was high, no further analysis was necessary. If confidence was medium or low, then two additional plots were drawn. The first was the ventilatory equivalent for O_2 and CO_2, ($\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$) versus $\dot{V}O_2$ (Fig. 3-3, panel C). In this plot, the GET was identified by an increase in the $\dot{V}_E/\dot{V}O_2$ ratio without a concomitant increase in the $\dot{V}_E/\dot{V}CO_2$ ratio. Secondly, a plot of $\dot{V}_E$ versus $\dot{V}O_2$ was drawn in which the first increase in $\dot{V}_E$ was defined as the GET (Fig. 3-3, panel D). Collectively, these four plots were used to accurately identify the GET and RCP from which exercise work rates for subsequent tests were calculated.

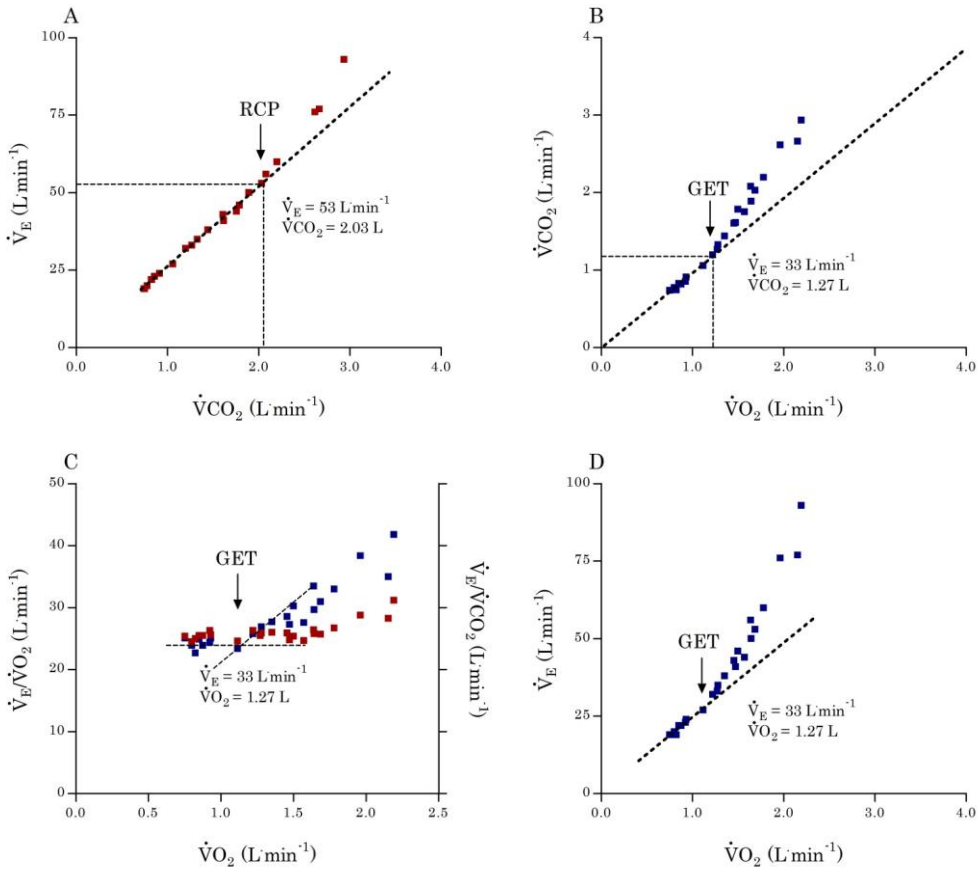

Fig. 3-3: Multiple parallel scatter plots used in the identification of GET and RCP for exercise work rate. Panels A & B are drawn initially, with additional plots C & D if confidence in the correct identification of GET is medium or low. See text for description. Representative data. ▪$\dot{V}O_2$, ▪$\dot{V}CO_2$.

3-5 Intra-Thoracic Pressure Measurements

Chapter 4 used a standard latex balloon-tipped catheter (Ackrad Labs, Cooper Surgical, Berlin, Germany) for the assessment of oesophageal (pleural) pressure (Poe). Chapters 5 and 6 used a multi-pair oesophageal electrode catheter (Bespoke Design, Gaeltec Devices Ltd, Isle of Skye, Scotland) which recorded oesophageal and gastric pressure (Pga) with transdiaphragmatic pressure (Pdi) calculated online by subtracting Poe from Pga. The electrode catheter was also used in the assessment of diaphragm electromyographic activity, discussed separately. Both catheters detected changes in intra-thoracic pressures that result from contractions of respiratory muscles but did so via different methods. While the distal end of the balloon catheter was fed into an independent pressure transducer (described below), the multi-pair electrode catheter used pressure transducers integrated into the catheter shaft. The pressure signal from both catheters was ultimately fed into an analogue-to-digital converter (1401, Cambridge Electronic Design, Cambridge, UK) and a signal amplifier (1902, Cambridge Electronic Design, Cambridge, UK), processed with a gain of 1000 Hz, and sampled at a frequency of 150 Hz.

3-5.1 Latex Balloon Catheter

The catheter consisted of an 86 cm long polyethylene tubular shaft (Fig. 3-4). At the proximal end of the catheter was a 9.5 cm long latex balloon which was positioned in the oesophagus using techniques to be described. The catheter included a lumen into which a metallic guide wire had been placed to aid in positioning, after which the guide wire was removed. The catheter was connected to a differential pressure transducer (model DP45, Valadyne, Northridge, CA; range ± 229 cmH_2O). The proximal end of the catheter contained multiple holes which aid in pressure detection. The holes are prevented from being occluded by the partially inflated latex balloon. When pressure is changed in the airway due to contractions of the respiratory muscles resulting in a change in airflow, the balloon deforms and transmits a pressure signal to the external transducer. The balloon must be inflated enough to allow such deformation, but not so much as to impart an initial signal which will result in an error in the zero pressure signal. The air volume must be sufficient so that the balloon will not be emptied at the maximum applied pressure thus creating an artificial ceiling. This can be an issue for gastric balloons, but less so for oesophageal. Furthermore, on compression due to a changing pressure wave, the air in the balloon, the catheter shaft and pressure transducer must convey a rising pressure signal resulting in a slight lag in the signal presented to the amplifier and is also true for a falling pressure. The transducer was calibrated across the physiological range. Briefly, the transducer and an electromanometer (model C9553, JMW, Harlow, UK) were connected via plastic tubing and a three-way valve into which a 10 ml glass calibration syringe was inserted. Pressures were manually applied to both the

transducer and electromanometer in 10 cmH_2O increments across the physiological range (−250 - 250 cmH_2O), and reference values for the transducer recorded against the electromanometer. The measurement of intra-thoracic pressures using this technique has been widely validated (Baydur, Behrakis, Zin, Jaeger & Milic-Emili, 1982; for review see, Benditt, 2005).

Calculating the Signal Delay

The propagation time of the external pressure signal from balloon to transducer was calculated. This allowed any observable delay to be compensated for with a time-shift process, thus allowing pressure measurements to be aligned with those of volume and flow. Two independent pressure transducers were attached to the proximal and distal ends of the catheter, and encased in two tubular deconnectors exhibiting an opening at the balloon-end. Following the application of a single external pressure to the balloon, transducer 1 at the proximal end displayed an instantaneous signal, whilst distally the transducer experienced a short delay. The pressure signal was acquired and analysed using numerical computation software (MatLab v7.14, MathWorks, Cambridge, UK), with three independent tests inducing a mean delay of 0.036 s.

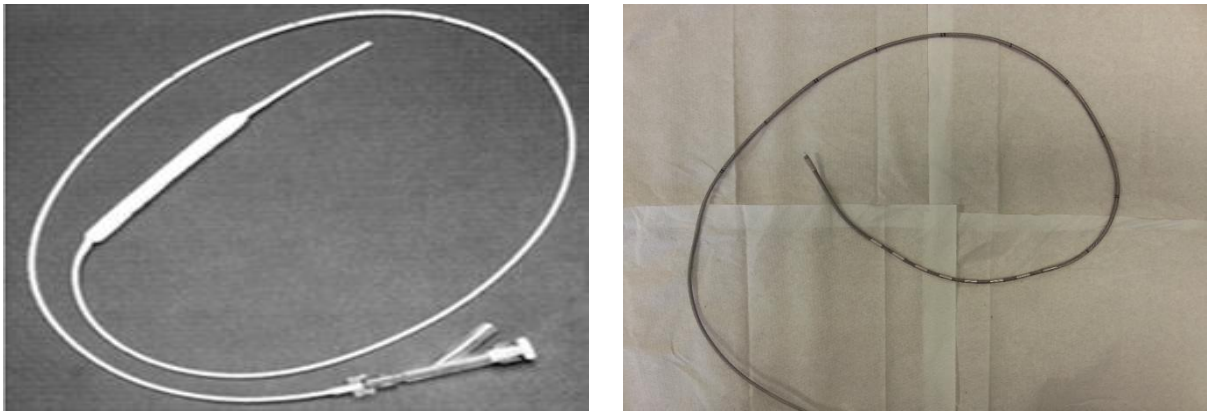

Fig. 3-4: Balloon catheter (left) which was used in Chapter 4 and a multi-pair oesophageal electrode catheter (right) which was used in Chapters 5 and 6.

3-5.2 Multi-Pair Oesophageal Electrode Catheter

The multi-pair electrode catheter (Gaeltec Devices Ltd, Isle of Skye) comprised a 100 cm silicon shaft (2.7 mm diameter) with 7 platinum electrodes spaced 1 cm apart and a metal diaphragm pressure transducer integrated into the catheter proximally and distally to the electrodes (Fig. 3-4). The pressure transducers use a metal diaphragm (1.6 x 4.0 mm) with a vacuum-deposited ceramic insulating layer and thin-film strain gauge on one side. The bonding between the metal substrate and the strain gauge, together with the low mass, result in a much higher recording frequency than can be achieved by larger, extra corporal sensors. A 150 Hz recording frequency was used in this thesis to match that of the volume and flow channels. The advantage of metal diaphragm sensors is that the signal is sent directly to the amplifier without the delay of routing via the transducer and without the signal degradation that can sometimes occur when using air or saline-filled catheters. Following a pressure change resulting from a contraction of the respiratory muscles, the diaphragm deformed and the signal was propagated directly to the amplifier and analogue-to-digital converter. Prior to each use, the catheter was calibrated across the physiological range (−250 - 250 cmH_2O) using a bespoke calibration tube (Gaeltec Devices Ltd, Isle of Skye) into which the catheter was inserted and then sealed at one end. A 10 ml glass syringe was connected to the calibration tube creating a vacuum and pressures were applied to the integrated transducers using the methods described above.

3-5.3 Positioning of Catheters

Prior to positioning of the catheter, participants applied < 1 ml topical anaesthetic gel (2% lydnocaine hydrochloride) to the nares, using a plastic syringe, to anaesthetise the nasal mucosa and pharynx. The catheter was passed pernasally into the stomach, facilitated by peristalsis from the swallowing of water sipped through a straw. When there was a positive pressure deflection on inspiration, resulting from contractions of the diaphragm, the catheter was slowly withdrawn until a negative oesophageal pressure deflection was observed during inspiration. The catheter position was validated using the occlusion technique described by Baydur *et al*. (1982). In Chapter 4, the balloon was inflated to a volume of 1 ml and the distal end connected to an independent differential pressure transducer. In Chapters 5 and 6, the catheter was passed pernasally into the stomach until the diaphragm produced a positive pressure deflection on inspiration, and re-positioned based on the strength of the diaphragm EMG signal (EMG_{di}) recorded simultaneously from different pairs of electrodes (Fig. 3-5). The catheter position was deemed to be optimal (electrode pair 3 positioned at the electrically active centre of the diaphragm) when EMG_{di} amplitude during inspiration was greatest in electrode pairs 1 and 3 with opposite polarity, and lowest in electrode pair 2 due to the cancellation of potential when both recording electrode pairs

were close to the source (Gandevia and McKenzie, 1986). The signal from the electrode pair exhibiting the largest amplitude was analysed using the quadratic mean (root mean square, RMS). In all instances, the catheter position was noted to ensure between-test consistency.

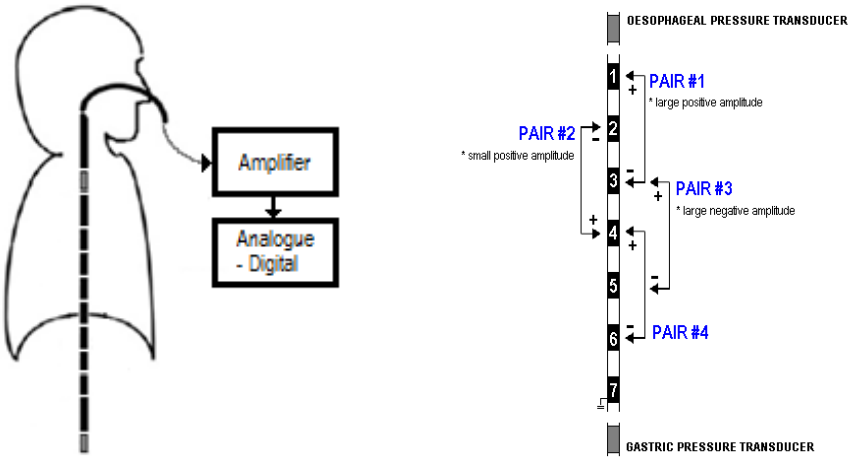

Fig. 3-5: Positioning and arrangement of the multi-pair oesophageal electrode catheter. Two pressure transducers were integrated into the catheter shaft proximally and distally to 7 platinum electrode coils. Pairs were arranged to be as close as possible to the electrically-active centre of the crural diaphragm.

3-6 Electromyography

Electromyography (EMG) is the experimental technique concerned with the development, recording and analysis of myoelectric signals (Konrad, 2005). EMG is used to record the electrical potential of a given muscle as nerve impulses propagate along the sarcolemma. Muscle fibres may become electrically-active from an external electrical stimulation (neurological EMG) or voluntary movements (kinesiological EMG). Within this thesis, two forms of kinesiological EMG were recorded: surface EMG of superficial abdominal muscles and deep EMG of the crural diaphragm. These two methods will be briefly discussed.

3-6.1 Multi-Pair Oesophageal Electrode Catheter

There are several methods by which diaphragm EMG may be recorded, including fine-wire needle electrodes, skin surface electrodes and oesophageal electrodes. Skin surface recordings of the costal diaphragm can be invalidated by signal contamination. Furthermore, the compound muscle action potential (CMAP) recorded from chest wall surface electrodes is likely to be contaminated by signals from adjacent muscles when the brachial plexus is co-activated, particularly when activating the diaphragm via phrenic nerve stimulation such as that used in Chapter 6 (Luo *et al.*, 1998; 1999). There may also be signal noise from the intercostals and abdominal muscles which are activated during breathing, and signal interference from subcutaneous fat (Beck, Sinderby, Weinberg & Grassino, 1995). Fine wire electrodes are impractical for most clinical or exercise studies, since electrodes are usually inserted between costal spaces and are, therefore, in close proximity to the lungs; this places the participant at risk of pneumothorax. As such, a single oesophageal electrode catheter fitted with several pairs of electrodes is considered the gold standard for EMG measurements of the crural diaphragm, although several potential sources of measurement error must be considered (Luo, Moxham, & Polkey, 2008).

The oesophageal catheter used for measurement of crural diaphragm activity in this thesis was based on a design originally used in research in the 1960s (Agostoni, Sant'Ambrogio & del Portillo Carrasco, 1960; Petit, Milic-Emili & Delhez, 1960). The bespoke catheter comprised a 100 cm silicon shaft (2.7 mm diameter) with 7 platinum electrodes spaced 1 cm apart. Although materials for the electrodes have included stainless steel, copper and silver, we preferred platinum electrodes due to their stability and slow degradation rate. The placement and positioning of the catheter is described above (see *Positioning of Catheters)*. There are two common problems with diaphragm EMG measures from oesophageal catheters: power line artefact and ECG artefact. A power line artefact originates from the power line and mains power equipment. It typically has a signal of 50 or 60 Hz depending on the power source. Proper earth connections and using a

differential amplifier with a high common mode rejection ratio (e.g. > 100 dB) can help in artefact reduction. In the measurements made in Chapter 5 and 6, we used an isolated pre-amplifier with a notch-filter, specifically designed for the removal of power line artefact. Notch filtering is the most commonly used technique for suppression of power line and harmonic interference that often contaminate EMG signals (Li, Rymer, Li & Zhou, 2011).

Removing the ECG Artefact

The diaphragm EMG frequency is from 20 – 250 Hz, whereas most of the ECG frequency is 0 – 100 Hz (Schweitzer, Fitzgerald, Bowden & Lynne-Davies, 1979). It is difficult, therefore, to eliminate the ECG effectively using filters due to the overlap in frequency. Many techniques have been used for analysing the EMG data with the ECG artefact; these include gating techniques, and the analysis of EMG data in-between the artefacts using markers that are triggered by the QRS complex. The technique adopted in this thesis was to use a programming script procedure within data acquisition software to eliminate the ECG artefact. Briefly, the script eliminates a manually determined region of data based upon the time duration of the QRS complex. Once the peak of the QRS complex has been manually identified, the user is required to specify the distance before and after the peak from which to remove a number of data points. For example, if the ECG artefact has a total duration of 0.1 s, then the number of data points to be removed is 400, since the sampling rate is 4000 Hz. The algorithm then used linear interpolation to predict future (or past) data values based on the assumption that the data is statistically stationary. The script generates a set of coefficients that when applied to the previous 'n' data points, generates the next predicted set of points.

3-6.2 Skin-Surface EMG

Different surface EMG systems were used in Chapters 4 and 6, both of which operate on the same principle. Electrodes were placed over the skin of the main belly of the relevant muscle. The depolarisation – repolarisation cycle that forms the basis of muscle excitation-contraction coupling, creates a depolarisation wave or 'electric dipole' which travels along the surface of the muscle fibre where it is detected by the electrical pair. An increasing potential difference is measured between the electrodes. Because a motor unit consists of many muscle fibres, the electrode pair 'see' the magnitude of all innervated fibres within this motor unit - depending on their spatial distance and resolution. Because the action potential arrives at the electrode of a bipolar pair at different times, the signal appears biphasic (Fig. 3-6).

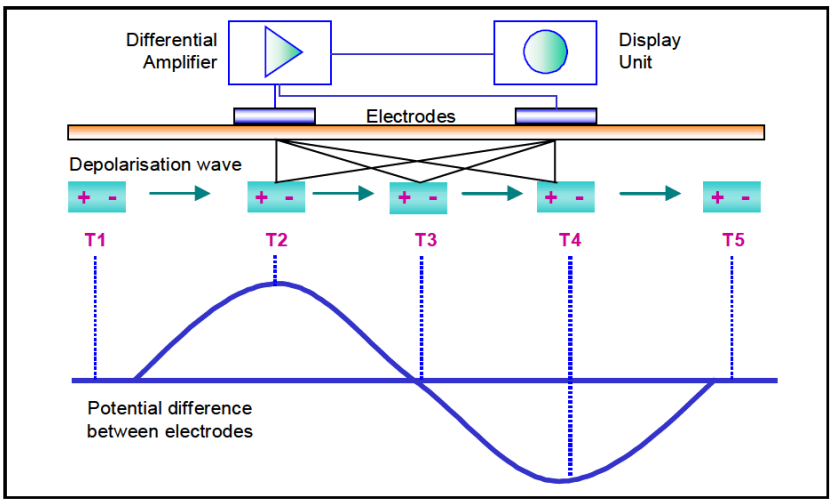

Fig. 3-6: The pattern of an electrical dipole on a muscle fibre membrane (Konrad, 2005)

In this thesis, surface EMG of the rectus abdominis was recorded using skin surface electrodes in Chapter 4 (Arbo Infant Electrodes, Tyco Healthcare, Germany) and wirelessly in Chapter 6 (Trigno Lab, Delsys Inc, Natick, Massachusetts). In both instances, the electrodes were positioned on the main belly of the muscle, 2 cm superior and 2 - 4 cm lateral to the umbilicus on the right-hand side of the torso. Electrodes were placed in the same orientation as the muscle fibres, i.e. inferolaterally, approximately 8° to the midline (Ng *et al.*, 1998) and secured to the skin using surgical dressing (Tegaderm Dressing, 3M, St. Paul, Minnesota). Prior to electrode placement, the localised area of skin was epilated, abraded with rough paper to remove dead skin cells and cleaned with alcohol to expel dirt and sweat (Cram and Rommen, 1989).

3-7 Data Acquisition and Analysis

Cardiorespiratory responses, intra-thoracic pressures and electromyography were sampled and recorded via the methods previously described. These indices of physiological function were combined using integrated data acquisition software (Spike 2 version 7.00, Cambridge Electronic Design) so that digital waveforms at rest or during exercise could be analysed simultaneously. The volume signal time lag, i.e. the time taken for the signal to be transmitted from the transducer sampling at the mouth to the digital waveform on the screen, was calculated during the initial calibration of the online system and then manually adjusted onscreen using a time-shift processing script that was integrated into the data acquisition software.

3-8 Operating Lung Volumes and Ventilatory Constraint

In Chapter 4, the prevalence and magnitude of ventilatory constraint was estimated by measuring dynamic changes in operating lung volumes, i.e. end-expiratory lung volume (EELV), end-inspiratory lung volume (EILV), the degree of flow limitation and the available inspiratory reserve volume (IRV) (Johnson, Weisman, Zeballos & Beck, 1999). EELV was calculated by asking participants to perform a maximal inspiratory capacity (IC) manoeuvre. The IC manoeuvres were performed in duplicate at rest and during the final 30 s of each exercise stage. Approximately 10 s prior to each manoeuvre, participants were given the following instruction: "at the end of a normal breath out, take a fast, maximal breath in to the top of your lung capacity". Following a further 5 – 10 spontaneous breaths, participants were asked to repeat the manoeuvre. Verbal encouragement was given to ensure a maximal inspiratory effort was made. The Poe associated with IC manoeuvres was checked against those produced during exercise and at rest to ensure maximal inspiratory efforts had been made in all conditions. Assuming that TLC is unaffected by exercise (Stubbing, Pengelly, Morse & Jones, 1980), then changes in the IC represented changes in EELV (TLC - IC). EILV was calculated by adding V_T to EELV.

To assess the degree of expiratory flow limitation, average spontaneous flow-volume loops were obtained at rest and in the last 30 s of a given exercise stage and then referenced against the maximal expiratory flow-volume (MEFV) envelope. To create the average flow-volume loop, 30 s of data was manually filtered to remove breaths that did not cross the line of zero flow, or those that were outside the upper- or lower-limit of three standard deviations of the mean volume. The remaining breaths were then averaged using script procedure (Spike 2 version 7.00, Cambridge Electronic Design, Cambridge, England) to create a single flow-volume loop that was representative of exercise. The degree of EFL was defined as the percent of the tidal flow-volume loop that encroached or exceeded the expiratory portion of the corrected maximal expiratory flow-volume curve (Johnson *et al.*, 1999).

3-8.1 Correcting for Thoracic Gas Compression and Exercise-Induced Bronchodilation

By superimposing exercise tidal breaths on a pre-exercise forced vital capacity (FVC) manoeuvre, the extent of EFL during exercise may be overestimated or falsely detected (Guenette *et al.*, 2010). This is because maximal expiratory manoeuvres may restrict expiratory flow. Ingram and Schilder (1966) compared FVC volume measurements at the mouth with those measured in a body displacement plethysmograph. They found that the volume signal recorded a larger volume of gas in the lung when measured at the mouth. Therefore, the volume-related flows at 25 and 50% of VC were lower in comparison to the plethysmograph, leading to the underestimation of flow. Additionally, exercise has been shown to have a bronchodilatory influence on the respiratory airways. Maximal expiratory flows at 50% of vital capacity are increased significantly in healthy male endurance athletes following exercise (Johnson *et al.*, 1992) which may result in greater flows post-exercise than those generated pre-exercise. To correct for exercise-induced bronchodilation and the flow-limiting effects of dynamic airway compression, participants were asked to perform several standard VC manoeuvres at subjective percentages of maximum effort (Guenette *et al.*, 2010), i.e. 20, 40, 60, 80 and 100%. Participants also performed maximal FVC manoeuvres pre- and post-exercise according to standard ATS/ERS procedures (Miller *et al.*, 2005). A new MEFV curve was thus created from the highest instantaneous flow-rate observed during any one of the several maximal and submaximal pre- and post-exercise vital capacity manoeuvres (Fig. 3-7). All manoeuvres were performed at resting baseline and within 4 min of exercise cessation.

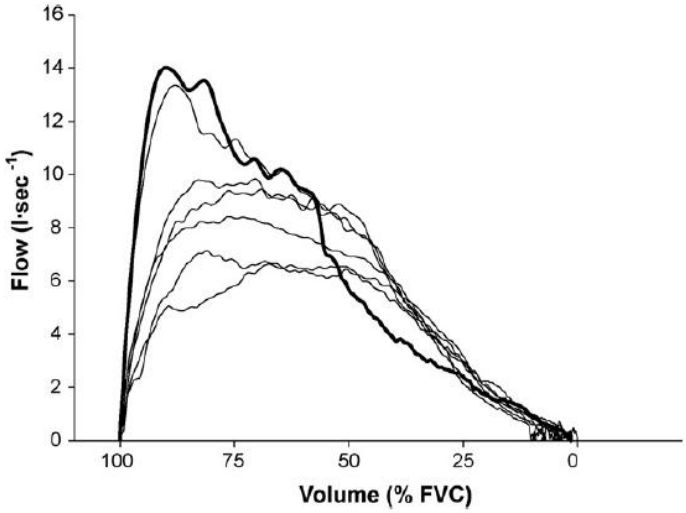

Fig. 3-7: Correcting for thoracic gas compression without using a pressure-compensated body-plethysmograph. Participants performed a traditional FVC manoeuvre (thick line) followed by several VC expirations at various submaximal efforts. A trace is then superimposed to follow the highest flow at any given volume and represents the new MEFV envelope. (Guenette *et al.*, 2010).

3-9 Nerve Stimulation

Magnetic stimulation was used in chapter 6 of this thesis in order to artificially stimulate the phrenic and thoracic nerve roots of the respiratory muscles from the central spinal foramina. Stimuli were delivered using a monophasic magnetic stimulator (Magstim 200, The Magstim Company Ltd., Whitland, Wales). A circular 90 mm coil was positioned at the cervical or thoracic spinal nerve roots to discriminate between the inspiratory and expiratory muscles, respectively, and activated at 100% stimulator capacity when participants were rested at FRC. A brief summary of the technique is presented below.

3-9.1 Assessing Respiratory Neuromuscular Function

Ugawa *et al*. (1989) reported that one could activate spinal nerves by magnetically inducing a current at the cervical or lumbosacral spinal enlargements, using a metallic coil which is placed at the spinal nerve roots that innervate the peripheral muscles of relevance (Fig. 3-8). In the present context, the relevant nerves for the inspiratory muscles are located from the 3rd to 5th cervical vertebrae (C_3 – C_5), which predominantly innervate the diaphragm but also other accessory inspiratory muscles including the scalenes and sternocleidomastoids (Fig. 3-9). Locating the appropriate vertebral region can be problematic. In 73% of human males, the most prominent spinous process is C_7, while in the other 27% it is T_1 (Grivas, Tsilimidos, Verras, Botsios & Chatzisaroglou, 2013). A majority of females present with a more prominent T_1. Since all participants participating in the current thesis were male, the most prominent spinous process was assumed to be the seventh cervical vertebrae. The 8th to 11th thoracic spinal nerve roots were stimulated to target the rectus abdominis, but conductance spread also results in stimulation of accessory expiratory muscles including the internal intercostals and transverse abdominis. On activation of the stimulator, a powerful and rapidly changing electrical current passes along the wound coil inducing an equally rapidly changing magnetic field (Matsumoto *et al.*, 2013). In accordance with Faraday's law, the magnetic field penetrates the coil and produces an induced current at the spinal neural foramina. This 'eddy' current propagates the membranes of the motor-neurons causing depolarisation of the axon and a subsequent action-potential. In this way the peripheral nervous system becomes activated without any current being passed through the participant's skin. Unlike its electrical predecessor, magnetic stimulation is thus painless and well-tolerated (Similowski *et al.*, 1988; 1989).

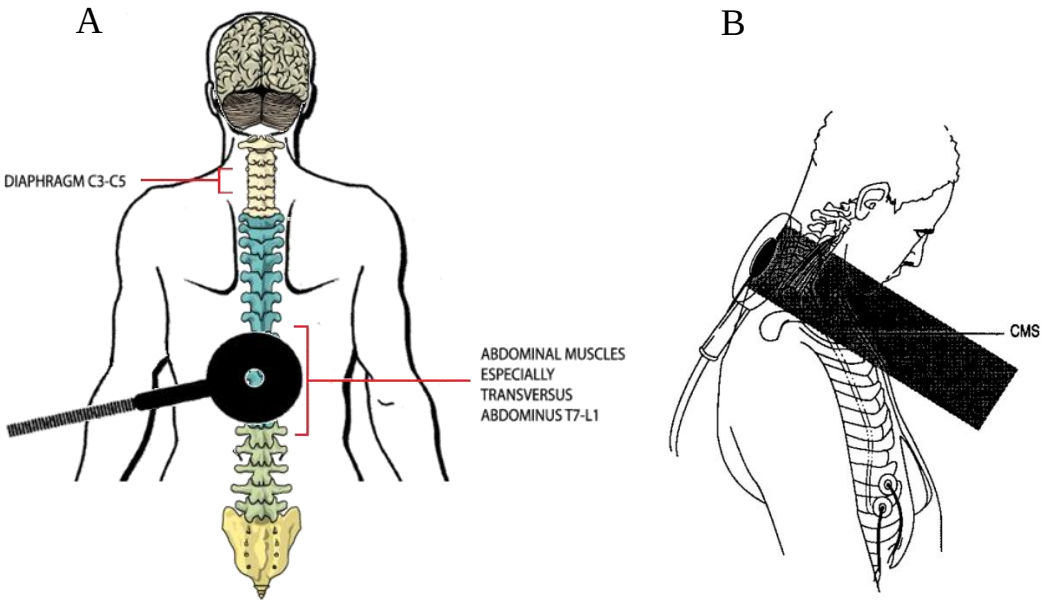

Fig. 3-8: Positioning of the 90 mm circular coil at the central thoracic nerves (A) and cervical nerves (B). The grey area is a schematic representation of the magnetic field (ATS/ERS, 2002).

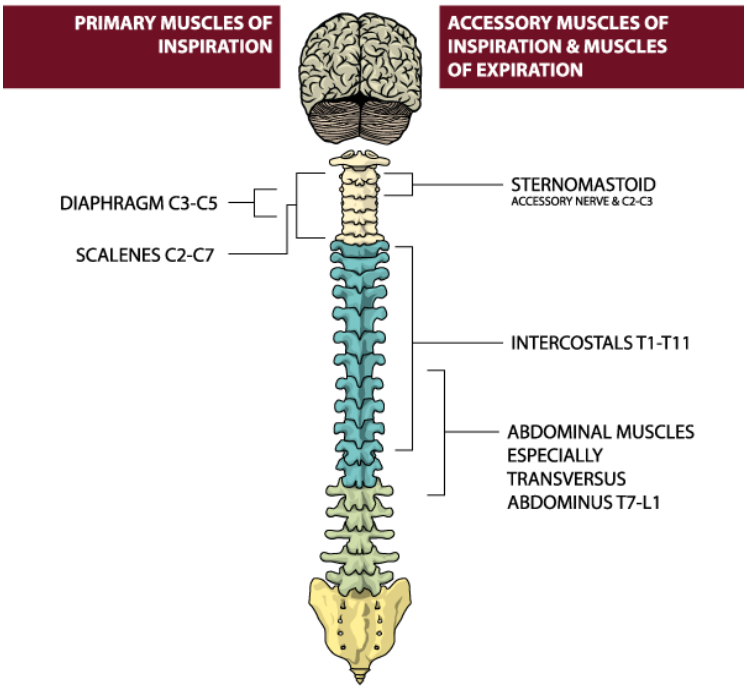

Fig. 3-9: A detailed schematic of the primary nerves innervating the respiratory muscles. In Chapter 6, the cervical and thoracic nerve roots were stimulated using magnetic stimulation. Image courtesy of Ontario Neurotrauma Foundation, (2012).

3-10 Pulse Oximetry

The functional saturation of arterial haemoglobin with oxygen (SpO_2) was estimated using a pulse oximeter (OxiMax N-560, Nellcor, Tyco Healthcare, Pleasanton, CA) and forehead SpO_2 sensor (Nellcor, Tyco Healthcare). The oximeter probe consisted of a light emitting diode (LED) and a photodiode detector which was applied to a pulsating arteriolar vascular bed, i.e. forehead. Pulse oximetry is based on two fundamental principles. First, that oxyhaemoglobin and deoxyhaemoglobin differ markedly in their capacity to absorb red and infrared light, i.e. oxygenated blood absorbs red light at 660 nm, whereas deoxygenated blood absorbs infrared light at 940 nm (Wukitsch, Petterson, Tobler & Pologe, 1988). Second, that the volume of arterial blood in tissue (and hence, light absorption by that blood) changes during the pulse. To determine SpO_2, red and infrared light was passed into the arteriolar bed and changes in light absorption during the pulsatile cycle was measured. The light sources were sequenced on and off, thus allowing a single detector to be used for both light sources. The amount of red and infrared light absorbed by blood was related back to the sensor and used to estimate to the haemoglobin content of the blood. (Nellcor, 2006). To compensate for differences in tissue thickness, the light intensity of the device's LED sensor was automatically adjusted. The measurement of oxygen saturation using forehead pulse oximetry has been validated, and has greater precision than finger sensors (Yamaya, Bogaard, Wagner, Niizeki & Hopkins, 2002).

3-11 Cardiac Frequency

A short-range telemetry system (Vantage NV; Polar Electro Oy, Kempele, Finland) was used to continuously monitor cardiac frequency (f_C). The system comprised two parts: a transmitter that was fitted inferiorly to the sternum against the skin and a wrist-watch receiver. The transmitter detected cardiac systole and sent an electromagnetic signal to the receiver which displayed heart rate. The measurement of cardiac frequency by telemetry has been validated (Terbizan, Dolezal & Albano, 2002).

3-12 Data Capture

Volume, flow, pressure and EMG signals were fed through an analogue-to-digital converter (1401, Cambridge Electronic Design) and signal amplifier (1902, Cambridge Electronic Design). The 4 EMG_{di} channels were filtered with a high common-mode rejection ratio (> 100dB), and a high pass filter of 50 Hz. Notch filters of 50 Hz were also applied on the isolated amplifier to further minimise mains signal artefact. Unless otherwise stated, physiological indices were averaged over a 30 s period.

Chapter Four

BREATHING MECHANICS DURING UPPER- VERSUS LOWER-BODY EXERCISE IN HEALTHY HUMANS

ABSTRACT

Introduction: There are unequivocal differences in the cardiorespiratory responses to upper- vs. lower-body exercise. Despite a paucity of studies assessing the mechanical-ventilatory responses, however, there is evidence to suggest that respiratory mechanics may be compromised during UBE. **Aim:** To characterise the mechanical-ventilatory responses to upper- vs. lower-body exercise in healthy humans. **Methods:** Breathing patterns, operating lung volumes, oesophageal pressure swings, EMG-derived measures of neural respiratory drive (rectus abdominis) and cardiorespiratory responses were assessed in 8 recreationally-active men (24 ± 5 [S.D.] y) during maximal graded upper-body exercise (UBE, arm-cranking)) and lower-body exercise (LBE, leg-cycling) performed in a randomised and counterbalanced order on separate days. Both exercise tests were performed to volitional fatigue and then repeated at work rates equivalent to 20, 40, 60, 80 and 100% of maximum arm ventilation ($\dot{V}_{EARM}$). **Results**: There was a significant constraint of tidal volume with upper-body vs. lower-body exercise at all percentages of $\dot{V}_{EARM}$ (2.0 ± 0.9 vs. 2.6 ± 0.7 L at 100%, $p < 0.001$). Tidal volume constraint was due primarily to an upward shift in end-expiratory lung volume ($p = 0.002$ at 100% $\dot{V}_{Earm}$) with limited evidence of expiratory flow limitation. Arm-cranking resulted in greater oesophageal pressure-derived measures of inspiratory muscle force output and greater EMG-derived measures of neural drive to the abdominal muscles at any given ventilation. **Conclusions**: Healthy participants exhibit constrained tidal volumes, relative dynamic hyperinflation and greater neural respiratory drive during arm-cranking relative to ventilation-matched leg-cycling. These responses are likely attributable, in part, to the competing roles of the respiratory muscles for ventilation, posture and locomotion during upper-body exercise.

4-1 Introduction

During lower-body exercise (LBE) of increasing work rate, healthy individuals meet ventilatory demand via the progressive recruitment of abdominal muscles to reduce end-expiratory lung volume (EELV), thereby increasing tidal volume (Sharratt *et al.*, 1987; Henke *et al.*, 1988; Grimby *et al.*, 1976; McClaran *et al.*, 1995). Dynamic reductions in EELV facilitate inspiration by optimising diaphragm length (Grimby *et al.*, 1976, Grassino *et al.*, 1981, Henke *et al.*, 1988) and by promoting elastic recoil of the abdominal wall (Grimby *et al.*, 1976, Grassino *et al.*, 1981). By contrast, upper-body exercise (UBE) results in lower tidal volumes (Takano *et al.*, 1993; Cerny and Ucer, 2004), elevated respiratory frequencies (Takano *et al.*, 1993; Cerny and Ucer, 2004; Hannink *et al.*, 2010) and a relative inability to reduce EELV (Alison *et al.*, 1998) compared to ventilation-matched LBE.

An increase in exercise EELV above baseline is defined as dynamic hyperinflation (Ferguson, 2006), and is typically exhibited by participants with obstructive lung disease (Hannink *et al.*, 2010; Grimby and Stiksa, 1970; Potter *et al.*, 1971; Dodd *et al.*, 1984; Stubbing *et al.*, 1980b; O'Donnell and Webb, 1993; Alison *et al.*, 1998). Increases in operating lung volumes in these populations may be the result of impending expiratory flow limitation (EFL) caused by diseased airways that partially collapse when thoracic pressures exceed a modest threshold. Ventilating at elevated lung volumes, decreases airway resistance and increases elastic recoil to aid expiration (Alison *et al.*, 1998; Porto *et al.*, 2009; Hannink *et al.*, 2010), and is, therefore, considered to be a compensatory mechanism, initiated to alleviate limitations to expiratory flow. A consequence of such respiratory mechanics, however, is a shortening of the inspiratory muscles which may exacerbate the elastic work of breathing (Milici-Emili and Petit, 1960). This may, in turn, elevate neural respiratory drive, which is strongly associated with elevated symptoms of respiratory stress (Celli *et al.*, 1985).

In a study assessing respiratory mechanics during constant-power arm-cranking in athletes with cervical spinal cord injury, substantial dynamic hyperinflation was observed during constant-power exercise (increased EILV and EELV). This may be due to the high (cervical) lesions that result in a complete dennervation of, and lack of control over, the major respiratory muscles. Furthermore, in a control group of healthy individuals, Alison *et al.* (1998) observed a relative inability of healthy participants to reduce EELV during arm-cranking. Importantly, neither study reported any evidence of EFL. It is unclear, therefore, if a dynamic increase in EELV is a typical response to UBE, or instead specific to obstructive lung disease and spinal cord injury.

It is likely that the alternative respiratory mechanics of UBE in healthy, able-bodied participants result from the specific locomotor characteristics of the task. Muscles of the thoracic cage have multiple functions including respiration, postural support and positioning of the arms (Hussain *et al.*, 1985). Furthermore, during upper-body exercise, the respiratory muscles are used to aid in stiffening the spine (Hodges *et al.*, 2005) and maintaining torso stabilisation (Celli, 1988). As such, UBE may result in additional loading of the respiratory muscles which may compromise respiratory function, and ultimately limit the ability of the organism to perform tasks requiring sustained heavy use of the arms (Cerny and Ucer, 2004).

A majority of studies on the physiological responses to arm-cranking have focused on participants with respiratory disease. These populations present with respiratory bronchiole thickening and excess mucous production on the gas exchange surface of the lung which negatively impacts on respiratory mechanics and exercise tolerance (Hogg and Timens, 2009). As a result, such studies may provide limited insight into the healthy responses to UBE. Respiratory mechanics have been assessed in healthy participants when replicating activities of daily living. In such investigations, unsupported arm exercise affected respiratory muscle recruitment and increased intra-thoracic pressures in a manner that was independent of metabolic demand or ventilatory drive (Celli, Criner & Rassulo, 1985; Couser, Martinez & Celli, 1992). The only studies making such measurements during dynamic, aerobic UBE in healthy participants (Alison *et al.*, 1998; Cerny & Ucer, 2004) have failed to assess changes in intra-thoracic pressures or respiratory muscle activation during exercise, both of which are essential in developing our understanding of the loads placed upon these muscles during UBE. The mechanisms that underpin the mechanical ventilatory responses to UBE, therefore, are still unclear.

Since individuals with COPD report an increased intensity of dyspnoea and exercise intolerance during activities requiring heavy use of the upper-limbs (Porto *et al.*, 2009; Colucci *et al.*, 2010) and breathlessness in tasks of daily living that utilise the upper-limbs (Tangi and Woolf, 1973; Celli, 1994), a further understanding of the UBE-induced limitations on respiratory function may inform clinical practice. Furthermore, research in this domain may have functional implications on athletic training programmes for those engaged in upper-body dependent sports, e.g. kayaking, rowing, swimming and disability sport.

4-1.1 Aims and Hypotheses

In light of the aforementioned considerations, this study aimed to characterise the respiratory mechanics and cardiorespiratory responses to dynamic UBE performed by a group of healthy

adults, and compared this to ventilation-matched LBE. Intra-thoracic pressure swings and EMG activity of the major expiratory muscles were assessed to inform our understanding of neural respiratory drive. It was hypothesised that UBE would result in lower tidal volumes relative to LBE at a given ventilation, necessitating increases in respiratory frequency. It was expected that UBE would elevate oesophageal pressure and abdominal muscle EMG due to additional roles of the respiratory muscles in postural support. Finally, it was hypothesised that UBE would result in a relative inability to reduce EELV compared to LBE.

4-2 Methods

4-2.1 Participants

Eight healthy, non-smoking, recreationally-active men between the ages of 18 – 35 y volunteered to participate in the study (mean ± S.D. age 24 ± 5 y, stature 1.79 ± 0.07 m, mass 74 ± 11 kg). All participants were free from cardiorespiratory disease. Furthermore, none of the participants had undergone systematic endurance or strength training for at least 4 months prior to the experiment. The study was approved by the institutional research ethics committee and written informed consent was obtained prior to data collection. Participants abstained from exercise for 48 h, alcohol and caffeine for 12 h, and food for 3 h prior to each visit.

4-2.2 Experimental Design

Participants underwent two maximal incremental exercise tests of upper-body exercise (UBE – arm-cranking) and two tests of lower-body exercise (LBE – leg-cycling). The first test with each modality was designed to elicit peak steady-state physiological responses, whereas the remaining two tests were designed to elicit similar minute ventilations (iso-ventilation). The order of upper- and lower-body tests were randomised and counterbalanced. The conditions could not be blinded, but participants were unaware of the experimental hypotheses. Cardiorespiratory responses and respiratory mechanics were assessed during all four tests, and expiratory flow limitation (EFL) was calculated at rest and during exercise using tidal flow-volume loops expressed against a maximal flow-volume envelope (see below). Each test was separated by at least 2 d, but no longer than 1 wk, and performed at a similar time of day in a comfortable, stable laboratory environment (mean ± S.D. temperature 22 ± 1°C, humidity 35 ± 9%, barometric pressure 757 ± 8 mmHg).

4-2.3 Baseline Pulmonary Function

Participants performed spirometry before and after each exercise test for the determination of the maximal expiratory flow-volume (MEFV) loop. Maximum static inspiratory and expiratory pressure manoeuvres were measured at the mouth (DP45; Validyne, Northridge, CA; range ± 229 cmH_2O) and performed from residual volume (RV) and total lung capacity (TLC), respectively (Green, Road, Sieck and Similowski, 2002). Spirometry was carried out according to recommended standards (Miller *et al.,* 2005).

4-2.4 Incremental Exercise Tests

The UBE trial was performed in the upright position using an electromagnetically-braked arm-crank ergometer (Angio; Lode, Groningen, The Netherlands). The ergometer was mounted to a wall and positioned so that the scapula-humeral joint and the distal end of the crank were horizontally aligned. Participants were instructed to keep their feet flat to the floor in order to prevent bracing. LBE was performed in the upright position using a cycle ergometer equipped with toe clips (Excalibur; Lode, Groningen, The Netherlands). The tests consisted of a steady-state resting period followed by continuous increments of 15 W (UBE) or 30 W (LBE) every 4 min. Higher cadence arm-cranking has been shown to elicit higher values for $\dot{V}O_{2peak}$ (Sawka *et al.*, 1983; Price and Campbell, 1997; Smith *et al.*, 2001; 2006a; Price *et al.*, 2007), with a freely-chosen cadence of 80 rev·min^{-1} seemingly optimal (Weissland *et al.*, 1997; Dekerle *et al.*, 2002; Smith *et al.*, 2007). The participants were, therefore, required to maintain a cadence of 75 - 80 rev·min^{-1} throughout all trials. Exercise was terminated when the cadence fell below 65 rev·min^{-1} for > 3 s despite strong verbal encouragement. The work rates for the iso-ventilation trials were established using inter-stage linear interpolation and set to 20, 40, 60, 80 and 100% of the peak ventilation obtained during the initial UBE test ($\dot{V}_{EARM}$; Fig. 4-1).

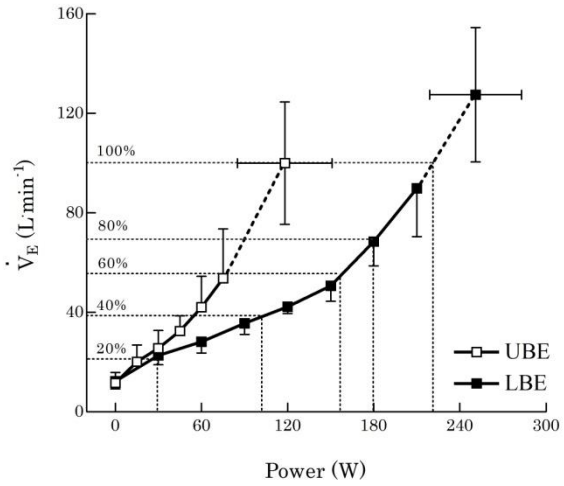

Fig. 4-1: Minute ventilation vs. power output for incremental UBE and LBE during visits 1 and 2. Work rates for subsequent visits were matched for ventilation using inter-stage linear interpolation and set to 20, 40, 60, 80 and 100% $\dot{V}_{EARM}$. Mean ± S.D. n=8.

4-2.5 Cardiorespiratory Measures

Continuous measurements of cardiac frequency (*f*c) were made by telemetry (Vantage NV; Polar Electro Oy, Kempele, Finland), arterial oxygen saturation (SpO_2) by forehead pulse-oximetry (OxiMax N-560, Nellcor, Tyco Healthcare, Pleasanton, CA) and ventilation and pulmonary gas exchange via online gas analysis (Oxycon Pro, Jaeger GmbH, Hoechberg, Germany). All measurements were averaged over the penultimate 30 s of rest and each exercise stage. Resting data during the UBE trials were collected while participants sat in an upright chair. Resting data during the LBE trials were collected while participants sat upright on the ergometer with the hands resting on the upper handlebars to prevent flexion of the trunk and excessive postural work of the thoracic muscles.

4-2.6 Expiratory Flow Limitation and Operating Lung Volumes

Expiratory flow limitation was calculated at rest and in the final 30 s of each exercise stage by measuring the percentage of the tidal flow-volume loop that met or exceeded the boundary of the MEFV curve (Johnson *et al.*, 1999). To correct for exercise-induced bronchodilation and the flow-limiting effects of dynamic airway compression, the MEFV curve was created from the highest instantaneous flow-rate observed during several maximal and submaximal pre- and post-exercise vital capacity manoeuvres performed at a subjective 20, 40, 60, 80 and 100% of maximum effort (Guenette *et al.*, 2010). All manoeuvres were performed at resting baseline and within 4 min of exercise cessation (see *General Methods)*. Within- and between-manoeuvre criteria for the attainment of FVC manoeuvres followed ATS/ERS guidelines (Miller *et al.*, 2005). Operating lung volumes (EELV and EILV) were calculated from duplicate inspiratory capacity (IC) manoeuvres performed from relaxation volume at rest and during the final 30 s of each exercise stage (Yan *et al.*, 1997). The IC manoeuvre exhibiting the most negative oesophageal pressure was used in positioning each tidal flow-volume loop within the corrected MEFV envelope.

4-2.7 Oesophageal Pressure

The oesophageal pressure swing during inspiration ($\Delta Poe_{,insp}$) was assessed using a latex balloon-tipped catheter (Ackrad Labs, Cooper Surgical, Berlin, Germany) connected to a differential pressure transducer (DP45; Validyne. range ±229 cmH_2O) that was calibrated across the physiological range using an electro-manometer (C9553, JMW, Harlow, UK). The catheter was passed pernasally into the stomach and inflated with 1 ml air. When the balloon detected a positive pressure deflection from the diaphragm upon inspiration, it was slowly withdrawn until a negative oesophageal pressure deflection was observed during inspiration. The balloon was then

withdrawn another 10 cm so that the distal end was situated in the lower one-third of the oesophagus (Benditt, 2005). The catheter position was validated using the occlusion technique (Baydur *et al.*, 1982). The tidal pressure swing during inspiration ($\Delta Poe_{,insp}$) was expressed in absolute terms and as a percentage of maximal Poe (P_{IMAX}) recorded during a Müller manoeuvre that was performed against a semi-occluded mouthpiece (Macintyre *et al.*, 2005).

4-2.8 Electromyography

Surface electromyography (EMG) was used to assess neural activation of the rectus abdominis (EMG_{ra}). A pair of 28 mm bipolar differential skin-surface electrodes (Arbo Infant Electrodes, Tyco Healthcare, Germany) were attached to the main belly of the muscle, 2 cm superior and 2-4 cm lateral to the umbilicus on the right-hand side of the torso (Ng *et al.*, 1998). Electrodes were placed in the same orientation as the muscle fibres, i.e. inferolaterally and ~8° to the midline, with a ground electrode positioned on the bony process of the anterior superior iliac spine (Ng *et al.*, 1998). Data were obtained at rest and during the final 30 s of each exercise stage. The EMG signal was passed through an analogue-to-digital converter (Micro 1401 mkII, Cambridge Electronic Design, Cambridge, England), high-pass filtered at 20 Hz and sampled at 4 KHz. Although previous studies have normalised EMG_{di} against the root-mean square (RMS) from a maximal mouth pressure manoeuvre (Vera-Garcia *et al.*, 2010), preliminary data suggested that the highest values for EMG_{ra} often occurred during peak dynamic exercise, possibly due to the combined ventilatory and postural demands of the activity. EMG_{ra} was, therefore, normalised against the highest single value achieved during the trial.

4-2.9 Statistics

Analyses were performed using SPSS 16.0 for Windows (SPSS Inc., IBM, Chicago, IL, USA). Peak exercise responses between UBE and LBE were compared using paired-samples t-tests. Differences in cardiorespiratory function ($\dot{V}O_2$, $\dot{V}CO_2$, RER, $\dot{V}_E$, f_R, V_T, f_C, SpO_2, $\dot{V}_E/\dot{V}O_2$ $\dot{V}_E/\dot{V}CO_2$, indices of respiratory duty cycle) and respiratory mechanics (EILV, EELV, IC, indices of Poe) between UBE and LBE at the various work rates were assessed using two-factor (mode * ventilation) repeated-measures ANOVA. Post-hoc analyses were conducted on significant mode by ventilation interactions using pairwise comparisons and Bonferroni adjustment. Alpha level was set at 0.05. Values were expressed as mean ± S.D.

4-3 Results

4-3.1 Participants

Participants exhibited healthy pulmonary function within normal limits (Table 4-1). Group mean maximal static pressures exceeded the age-predicted inspiratory (+35%) and expiratory (+6%) maximum values.

4-3.2 Peak Physiological Responses

Peak physiological responses to maximal incremental UBE and LBE are shown in Table 4-2. UBE resulted in significantly lower values for work rate ($p < 0.001$), $\dot{V}O_2$ ($p < 0.001$), $\dot{V}CO_2$ ($p < 0.001$), $\dot{V}_E$ ($p < 0.01$), V_T ($p < 0.001$). Peak O_2 uptake for UBE was ~77 ± 10% of the value achieved during LBE. There was a trend towards lower f_C in UBE ($p = 0.06$). LBE resulted in significantly elevated EELV ($p < 0.05$) and EILV ($p < 0.001$) at maximal exercise, but these differences diminished when normalised against the higher $\dot{V}_E$. There were no differences in Poe associated with IC manoeuvres at peak exercise (−70.3 ± 20.0 vs. −69.1 ± 27.0 cmH_2O), suggesting maximal inspiratory efforts had been made in both conditions. Despite higher $\dot{V}_{Epeak}$ during LBE, abdominal muscle EMG was substantially higher during UBE. There were no differences in $\Delta Poe_{,insp}$, RER, SpO_2, f_R, $\dot{V}_E/\dot{V}O_2$ or $\dot{V}_E/\dot{V}CO_2$ between peak UBE and LBE.

Table 4-1: Baseline pulmonary function

	Value			%Predicted		
FEV_1 ($L \cdot s^{-1}$)	4.35	±	0.42	97	±	12
FVC (L)	5.69	±	0.44	106	±	8
FEV_1/FVC (%)	77	±	7	93	±	8
IC (L)	2.8	±	3.1	-	±	-
MIP (cmH_2O)	158	±	17	135	±	18
MEP (cmH_2O)	166	±	40	106	±	27

Mean ± S.D. n=8. Predicted values for spirometry from Quanjer *et al.* (1993), maximal static pressures from Wilson, Cooke, Edwards & Spiro, (1984). FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; IC, inspiratory capacity; MIP, maximal inspiratory mouth pressure; MEP, maximal expiratory mouth pressure.

Table 4-2: Peak physiological responses to UBE versus LBE

	LBE			UBE		
Work rate (W)	251	±	32	118	±	33*
$\dot{V}O_2$ ($L \cdot min^{-1}$)	3.12	±	0.72	2.36	±	0.54*
$\dot{V}O_2$ ($ml \cdot kg \cdot min^{-1}$)	40.7	±	10	30.7	±	6.3*
$\dot{V}CO_2$ ($L \cdot min^{-1}$)	3.64	±	0.51	2.67	±	0.53*
$\dot{V}_E/\dot{V}O_2$	43	±	15	43	±	7.0
$\dot{V}_E/\dot{V}CO_2$	34.8	±	5.3	37.5	±	5.6
RER	1.22	±	0.30	1.14	±	0.08
$\dot{V}_E$ ($L.min^{-1}$)	127	±	27	100	±	25*
V_T (L)	2.60	±	0.59	2.03	±	0.42*
f_R ($br.min^{-1}$)	47	±	10	48	±	11
EILV (%FVC)	79	±	8	63	±	10*
EELV (%FVC)	32	±	8	27	±	10*
EMG_{ra} ($\%MVC_{RMS}$)	30	±	16	96	±	63
$\Delta Poe_{,insp}$ (cmH_2O)	-25.7	±	-5.2	-26.3	±	-8.7
f_C ($b \cdot min^{-1}$)	179	±	11	171	±	11
SpO_2 (%)	95.6	±	2.0	97.2	±	2.1

Mean ± S.D. n = 8. $\dot{V}O_2$, O_2 uptake; $\dot{V}CO_2$, CO_2 output; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for O_2; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for CO_2; RER, respiratory exchange ratio; $\dot{V}_E$, minute ventilation; V_T, tidal volume; f_R, respiratory frequency; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume, EMG_{ra}, electromyography rectus abdominis; $\Delta Poe_{,insp}$, tidal oesophageal pressure swing during inspiration; f_C, cardiac frequency; SpO_2, arterial oxygen saturation. *Significantly different versus LBE ($p < 0.05$).

4-3.3 Iso-Ventilatory Physiological Responses

Cardiorespiratory Responses

Cardiorespiratory responses to ventilatory-matched UBE versus LBE are displayed in Table 4-3. A primary aim was to match $\dot{V}_E$ between UBE and LBE at each progressive work rate. Values for UBE and LBE were not significantly different across work rates except at 60% $\dot{V}_{EARM}$ which was higher during cycling ($p < 0.01$, Fig. 4-2). Ventilation during UBE exercise at 20 – 80% $\dot{V}_{EARM}$ was achieved via increases in V_T and f_R, after which V_T plateaued from 80 - 100% $\dot{V}_{EARM}$. Respiratory frequency increased accordingly with the greatest differences at 100% $\dot{V}_{EARM}$ (Fig. 4-3). Despite similar $\dot{V}_E$ between UBE and LBE throughout, V_T was lower during UBE at all work rates ($p < 0.05$) and there was a trend towards higher f_R at 80 and 100% $\dot{V}_{EARM.}$ Differences in $\dot{V}O_2$ are shown in Fig. 4-3. Both $\dot{V}O_2$ and $\dot{V}CO_2$ were lower during UBE ($p < 0.05$) at all work rates above 60% $\dot{V}_{EARM}$. Respiratory exchange ratio and $\dot{V}_E/\dot{V}CO_2$ were not different at rest but tended to be higher during UBE with significant main effects ($p < 0.05$). Cardiac frequency tended to be lower during UBE exercise with a significant main effect ($p < 0.05$), but there were no differences in SpO_2 at any work rate. Oxygen pulse increased to a lesser extent during UBE and was generally lower during UBE across all work rates with a significant main effect ($p < 0.001$). Respiratory duty cycle tended to be shorter and mean inspiratory flow tended to be lower during UBE exercise, but differences diminished when adjusted for the difference in V_T. There were no differences in SpO_2 between UBE and LBE at any $\dot{V}_E$.

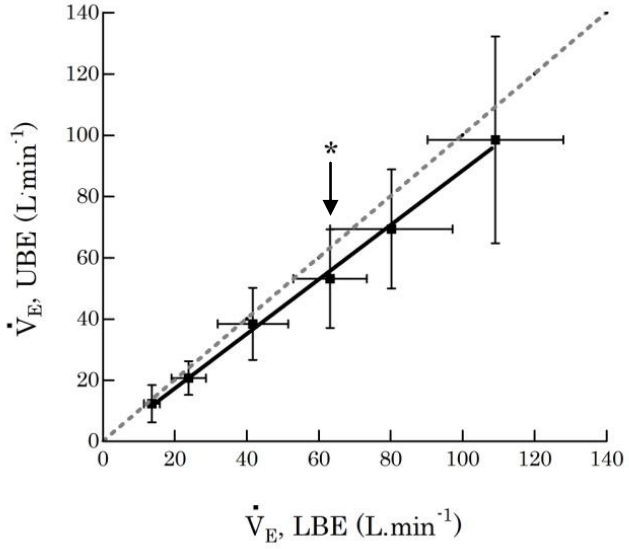

Fig. 4-2: Minute ventilation during incremental UBE vs. LBE at predetermined work rates. Ventilation is similar at rest and all exercise work rates with the exception of 60% $\dot{V}_{EARM}$. Mean ± S.D. n=8. *Significantly different from LBE ($p < 0.01$)

Table 4-3: Cardiorespiratory responses during incremental UBE vs. LBE at rest, 20, 40, 60, 80 and 100% maximal $\dot{V}_{EARM}$

	Rest		**20% $\dot{V}E_{ARM}$**		**40% $\dot{V}E_{ARM}$**		**60% $\dot{V}E_{ARM}$**		**80% $\dot{V}E_{ARM}$**		**100% $\dot{V}E_{ARM}$**	
	LBE	UBE	LBE	UBE	LBE	UBE	LBE	UBE	LBE	UBE	LBE	UBE
Work Rate (W)	0 ± 0	0 ± 0	26 ± 19	18 ± 12	111 ± 39	63 ± 24	168 ± 37	84 ± 25	199 ± 37	97 ± 29	221 ± 39	113 ± 30
$\%W_{max}$ (%)	0 ± 0	0 ± 0	10 ± 7	15 ± 10	44 ± 11	55 ± 13	67 ± 9	74 ± 7	80 ± 9	86 ± 6	89 ± 9	100 ± 0
$\dot{V}O_2$ ($L \cdot min^{-1}$)	0.51 ± 0.27	0.43 ± 0.08	0.99 ± 0.28	0.76 ± 0.21	1.72 ± 0.51	1.26 ± 0.35*	2.35 ± 0.53	1.69 ± 0.39*	2.76 ± 0.55	2.04 ± 0.52*	3.07 ± 0.62	2.38 ± 0.54*
$\dot{V}O_2$ ($ml \cdot kg \cdot min^{-1}$)	6.6 ± 3.4	5.7 ± 1.4	12.9 ± 3.3	10.1 ± 3.1	22.3 ± 5.6	16.3 ± 3.7*	30.6 ± 6.1	21.9 ± 4.0*	36.1 ± 6.5	26.4 ± 5.8*	39.7 ± 5.5	31.0 ± 6.5*
$\dot{V}CO_2$ ($L \cdot min^{-1}$)	0.45 ± 0.16	0.42 ± 0.09	0.91 ± 0.23	0.76 ± 0.15	1.68 ± 0.45	1.37 ± 0.34	2.43 ± 0.53	1.89 ± 0.34*	2.96 ± 0.60	2.25 ± 0.51*	3.42 ± 0.76	2.69 ± 0.55*
O_2 pulse ($ml \cdot beat^{-1}$) †	8.4 ± 4.7	6.9 ± 1.6	11.8 ± 3.4	10.3 ± 3.0	15.6 ± 4.4	12.2 ± 3.1	17.4 ± 3.6	13.0 ± 3.8	17.8 ± 3.5	13.8 ± 3.9	18.2 ± 3.9	14.3 ± 3.4
RER †	1.00 ± 0.51	0.98 ± 0.20	0.92 ± 0.09	0.99 ± 0.12	0.98 ± 0.06	1.10 ± 0.07	1.04 ± 0.04	1.14 ± 0.10	1.07 ± 0.04	1.11 ± 0.08	1.11 ± 0.05	1.13 ± 0.07
$\dot{V}_E/\dot{V}O_2$	27.9 ± 15.0	28.8 ± 3.8	24.6 ± 4.4	27.9 ± 4.9	24.5 ± 2.8	30.8 ± 2.6	26.8 ± 2.4	31.8 ± 2.8	28.8 ± 2.5	34.3 ± 4.0	35.0 ± 4.5	41.8 ± 4.8
$\dot{V}_E/\dot{V}CO_2$ †	30.3 ± 10.7	30.0 ± 6.2	26.7 ± 4.1	27.0 ± 2.6	24.8 ± 2.5	28.1 ± 3.2	25.8 ± 2.3	28.1 ± 2.4	27.0 ± 2.5	30.9 ± 3.4	31.5 ± 4.0	36.9 ± 4.2
$\dot{V}_E$ ($L.min^{-1}$)	13.7 ± 6.1	12.3 ± 2.1	23.9 ± 5.5	20.7 ± 4.8	41.7 ± 11.7	38.4 ± 9.8	63.2 ± 16.1	53.1 ± 10.3*	80.2 ± 19.5	69.4 ± 17.0	109.1 ± 33.8	98.5 ± 18.9
V_T (L)	0.87 ± 0.30	0.61 ± 0.25*	1.08 ± 0.40	0.92 ± 0.26*	1.75 ± 0.64	1.50 ± 0.66*	2.27 ± 0.68	1.74 ± 0.61*	2.52 ± 0.67	2.07 ± 0.70*	2.55 ± 0.72	1.97 ± 0.85*
f_R ($br \cdot min^{-1}$)	14.9 ± 3.8	15.2 ± 2.4	20.5 ± 4.2	18.8 ± 3.4	22.9 ± 2.4	24.4 ± 6.0	26.6 ± 3.3	27.2 ± 5.7	31.2 ± 5.2	34.3 ± 8.7	42.3 ± 11.4	48.4 ± 13.3
T_I (s)	1.75 ± 0.58	1.47 ± 0.28	1.21 ± 0.23	1.20 ± 0.20	1.16 ± 0.24	1.14 ± 0.26	1.04 ± 0.21	0.99 ± 0.23	0.94 ± 0.23	0.94 ± 0.24	0.78 ± 0.20	0.70 ± 0.23
T_E (s)	2.14 ± 0.79	1.91 ± 0.28	1.69 ± 0.32	1.66 ± 0.24	1.50 ± 0.36	1.49 ± 0.33	1.24 ± 0.27	1.19 ± 0.26	1.08 ± 0.26	1.06 ± 0.33	0.83 ± 0.24	0.69 ± 0.23
T_{TOT} (s)	3.88 ± 1.29	3.38 ± 0.50	2.89 ± 0.53	2.86 ± 0.40	2.66 ± 0.59	2.62 ± 0.58	2.28 ± 0.47	2.18 ± 0.48	2.02 ± 0.49	2.00 ± 0.56	1.61 ± 0.44	1.39 ± 0.45
T_I/T_{TOT}	0.45 ± 0.06	0.43 ± 0.04	0.42 ± 0.03	0.42 ± 0.03	0.44 ± 0.01	0.43 ± 0.02	0.46 ± 0.01	0.45 ± 0.02	0.47 ± 0.01	0.47 ± 0.03	0.48 ± 0.01	0.50 ± 0.03
T_E/T_{TOT}	0.55 ± 0.06	0.57 ± 0.04	0.58 ± 0.03	0.58 ± 0.03	0.56 ± 0.01	0.57 ± 0.02	0.54 ± 0.01	0.55 ± 0.02	0.53 ± 0.01	0.53 ± 0.03	0.52 ± 0.01	0.50 ± 0.03
V_T/T_I ($L \cdot s^{-1}$)	0.53 ± 0.19	0.42 ± 0.16	0.89 ± 0.22	0.77 ± 0.21	1.49 ± 0.35	1.31 ± 0.37	2.20 ± 0.51	1.76 ± 0.40	2.72 ± 0.60	2.23 ± 0.53	3.38 ± 0.87	2.85 ± 0.64
f_C ($breaths \cdot min^{-1}$) †	64 ± 10	63 ± 6	84 ± 7	75 ± 9	110 ± 13	104 ± 13	135 ± 16	133 ± 19	156 ± 14	150 ± 20	169 ± 12	167 ± 14
SpO_2 (%)	98 ± 2	99 ± 2	97 ± 3	99 ± 1	96 ± 4	98 ± 3	97 ± 3	98 ± 3	97 ± 2	98 ± 2	95 ± 3	98 ± 2

Mean ± S.D. n = 8. $\%W_{max}$, work rate expressed as a percentage of mode-specific maximum power; $\dot{V}O_2$, O_2 uptake; $\dot{V}CO_2$, CO_2 output; O_2 pulse, O_2 delivery per systole; RER, respiratory exchange ratio; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for O_2; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for CO_2; $\dot{V}_E$, minute ventilation; V_T, tidal volume; f_R, respiratory frequency; T_I, inspiratory time; T_E, expiratory time; T_{TOT}, total respiratory time; V_T/T_I, mean inspiratory flow; f_C, cardiac frequency; SpO_2, arterial O_2 saturation. *Significantly different versus LBE ($p < 0.05$). † Significant main effect for mode ($p < 0.05$).

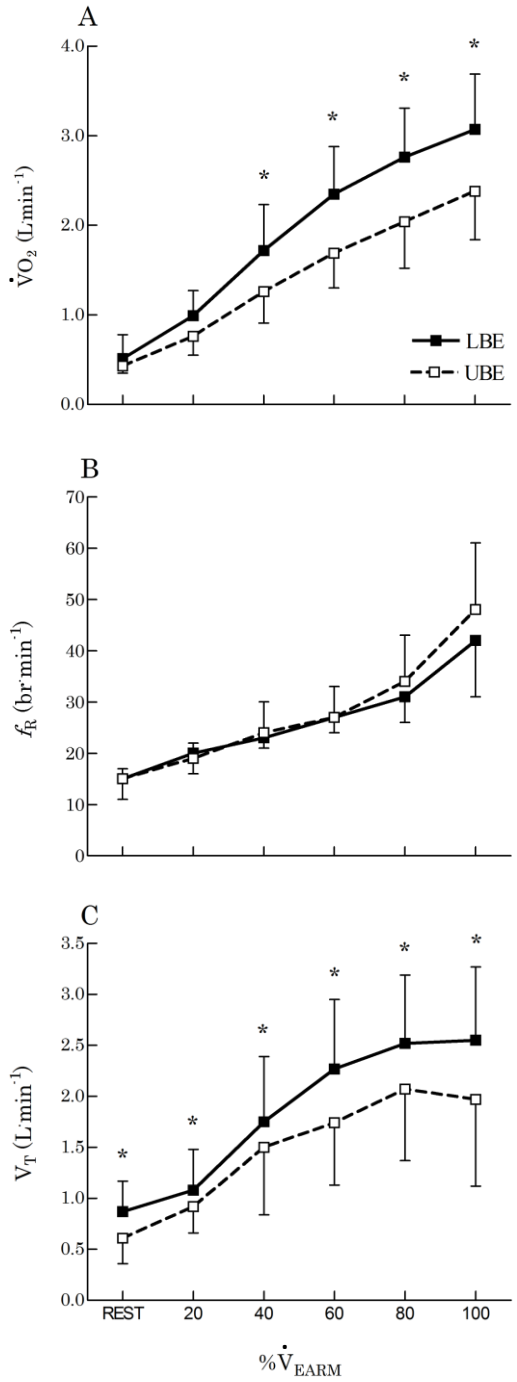

Fig. 4-3: Oxygen uptake (panel A), respiratory frequency (panel B) and tidal volume (panel C) during incremental UBE vs. LBE performed at iso-ventilations. Oxygen uptake was not different between trials at rest or 20% $\dot{V}_{Earm}$ but significantly lower during UBE at all other ventilations. Respiratory frequency tended to be higher during UBE at 80 – 100% $\dot{V}_{Earm.}$ Tidal volumes were lower during UBE at all work rates. Differences during resting V_T were likely due to differences in resting body position. Mean ± S.D. n=8. *Significantly different from LBE ($p < 0.05$).

Expiratory Flow Limitation and Operating Lung Volume

Operating lung volumes during iso-ventilatory UBE vs. LBE are shown in Fig. 4-4 and Table 4-4. During LBE, the increase in V_T with progressive work rate was achieved via increases in EILV and decreases in EELV. Tidal volume during UBE was achieved almost exclusively via increases in EILV from 20-80% $\dot{V}_{EARM}$, whereas EELV decreased below baseline at 20% $\dot{V}_{EARM}$ but increased steadily thereafter. At peak arm-crank intensities EELV increased significantly during UBE relative to LBE ($p < 0.01$), reflected by a lower inspiratory capacity (3.49 ± 0.53 vs. 4.01 ± 0.61 L). The mean oesophageal pressure swing exhibited during the IC manoeuvres were similar at all exercise ventilations ($p > 0.05$), suggesting that participants gave consistent inspiratory efforts. Two of eight participants exhibited EFL during LBE (Fig 4-5). In these participants, the magnitude of the tidal flow-volume loop that encroached on the MEFV envelope was 68 and 81% during LBE. The same participants exhibited EFL during UBE, albeit to a lesser extent (39 and 52%). Baseline pulmonary function was within normal limits for both participants. When the two participants were removed from the group mean data, the difference in EELV between UBE and LBE was not statistically affected, suggesting that the increase in EELV at peak exercise was independent of EFL.

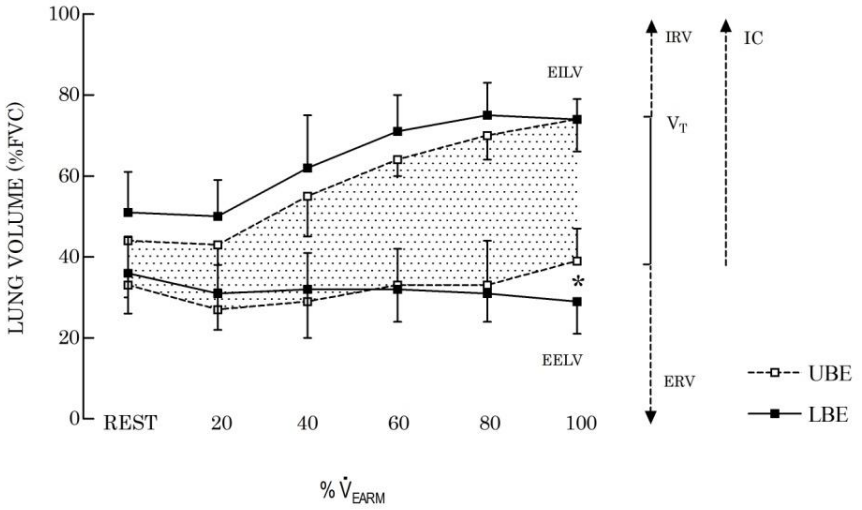

Fig. 4-4: Operating lung volumes during incremental UBE vs. LBE performed at iso-ventilations. End-expiratory lung volume (EELV) was similar between exercise modes until 100% $\dot{V}_{EARM}$ at which point EELV increased significantly during UBE. Mean ± S.D. n=8. *Significantly different from LBE ($p < 0.01$).

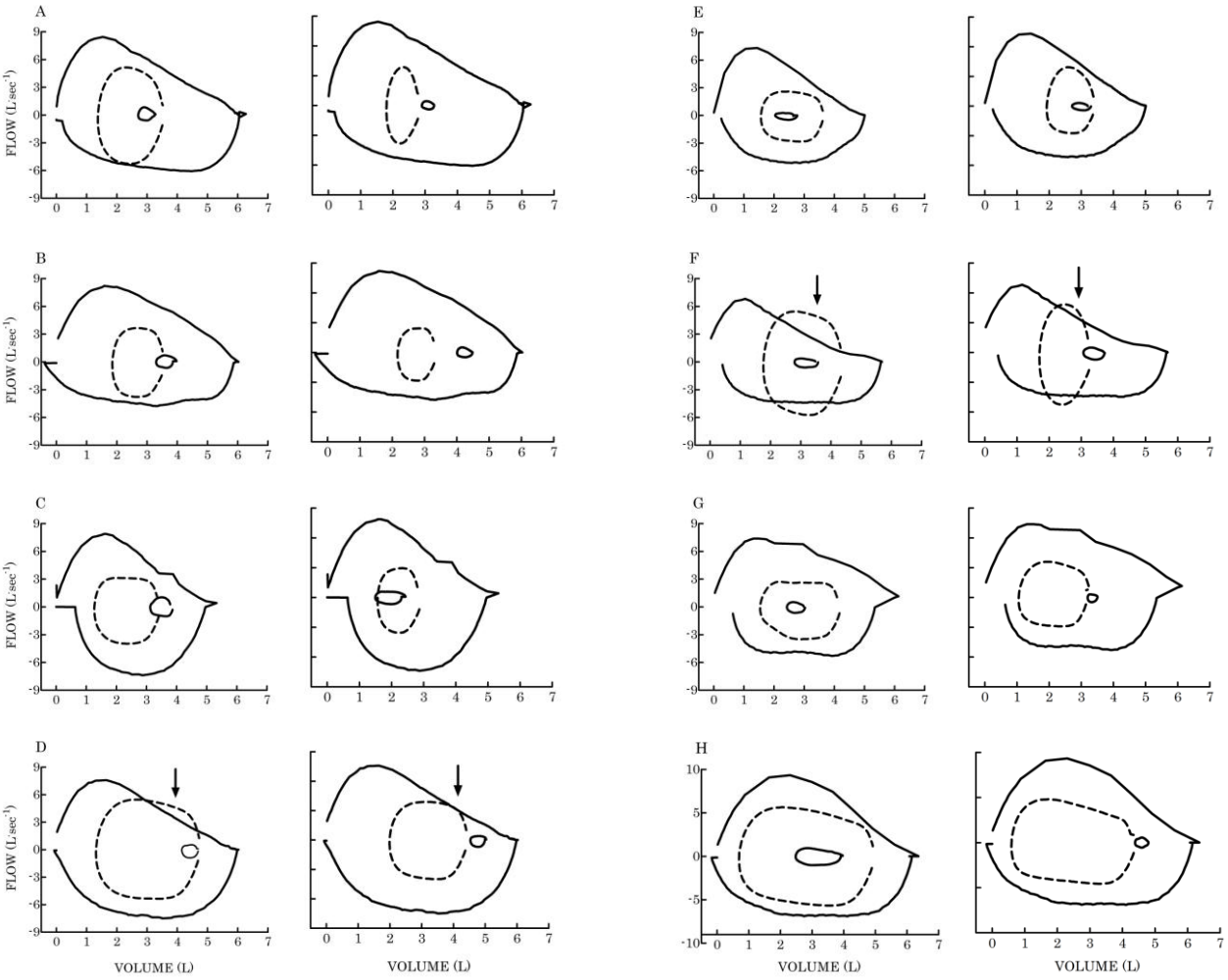

Fig. 4-5: Individual participant flow-volume loops (panels A – H) at rest and at 100% $\dot{V}_{EARM}$ for LBE (left column) and UBE (right column), positioned against the corrected MEFV loop. Two participants (panels D and F) exhibited EFL during both upper- and lower-body exercise (39 vs. 68% and 52 vs. 81%). Removing their data from calculations of EELV did not affect the magnitude of the difference.

Oesophageal Pressure and Abdominal Muscle EMG

Oesophageal pressure swings during inspiration expressed as a percentage of maximal static inspiratory Poe (Poe/P_{IMAX}) is shown in Fig. 4-6. Poe/P_{IMAX} was similar at rest but higher during UBE at all ventilations exhibiting a main effect difference ($p < 0.01$). Due to technical issues, electromyographic activity of the rectus abdominis was obtained from a subset of 3 participants during the last 30 s of each exercise stage. EMG_{ra} was higher during UBE at all ventilations relative to LBE (Fig. 4-6). While abdominal muscle activity during LBE remained fairly constant with increasing work rate, RMS increased substantially and proportionally with work rate during UBE.

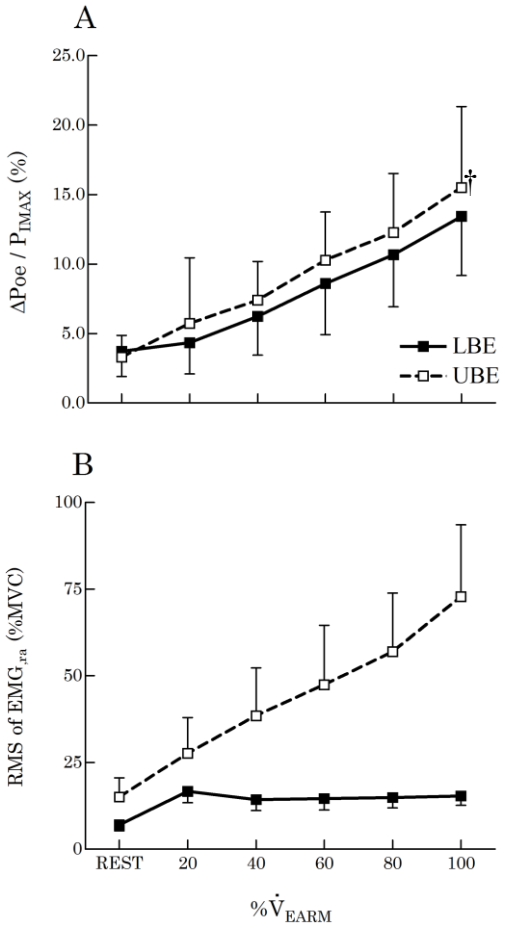

Fig. 4-6: Oesophageal pressure swings during inspiration expressed relative to maximal inspiratory pressure (panel A) and abdominal muscle EMG (panel B) during incremental UBE vs. LBE performed at iso-ventilations. Oesophageal pressure swings were not different at rest but greater during UBE at all exercise ventilations showing a main effect difference. Abdominal muscle EMG was greater during UBE at all ventilations and increased proportionally with work rate. Mean ± S.D. Poe/P_{IMAX} n=8, EMG n=3. †Significant main effect for mode.

Table 4-4: Respiratory Mechanics during incremental UBE vs. LBE at rest, 20, 40, 60, 80 and 100% maximal $\dot{V}_{EARM}$

	Rest		**20% $\dot{V}E_{ARM}$**		**40% $\dot{V}E_{ARM}$**		**60% $\dot{V}E_{ARM}$**		**80% $\dot{V}E_{ARM}$**		**100% $\dot{V}E_{ARM}$**	
	LBE	UBE	LBE	UBE	LBE	UBE	LBE	UBE	LBE	UBE	LBE	UBE
EILV (%FVC) †	51 ± 10	44 ± 14	50 ± 9	43 ± 11	62 ± 13	55 ± 10	71 ± 9	64 ± 4	75 ± 8	70 ± 6	74 ± 5	74 ± 8
EELV (%FVC)	36 ± 10	33 ± 12	31 ± 9	27 ± 11	32 ± 12	29 ± 12	32 ± 8	33 ± 9	31 ± 7	33 ± 11	29 ± 8	39 ± 8*
$\Delta Poe / P_{IMAX}$ (%) †	3.7 ± 1.8	3.3 ± 1.6	4.3 ± 2.2	5.7 ± 4.7	6.2 ± 2.8	7.4 ± 2.8	8.6 ± 3.7	10.3 ± 3.5	10.7 ± 3.8	12.3 ± 4.3	13.4 ± 4.2	15.5 ± 5.8
EMG_{ra} (%MVC)	7.0 ± 5	15 ± 17	17 ± 10	28 ± 31	14 ± 10	39 ± 4	15 ± 10	47 ± 52	15 ± 9	57 ± 51	15 ± 8	73 ± 62

Mean ± S.D. n=8. (EMG, n=3). EILV, end-inspiratory lung volume; EELV, end expiratory lung volume; IC, inspiratory capacity; $\Delta Poe/P_{IMAX}$, oesophageal pressure swing (inspiration) expressed relative to maximal oesophageal pressure; EMG_{ra}, electromyography of the rectus abdominis. *Significantly different from LBE. †Significant main effect for mode.

4-4 Discussion

This study assessed respiratory mechanics and cardiorespiratory function during UBE and LBE, performed by healthy, able-bodied men, at a range of ventilation-matched work rates. The principal findings were that UBE significantly constrained tidal volume relative to LBE at any given $\dot{V}_E$, and resulted in a significant increase in EELV at peak $\dot{V}_{EARM}$ with limited evidence of expiratory flow limitation. Furthermore, UBE induced significantly larger oesophageal-pressure swings and greater abdominal muscle EMG-derived measures of neural respiratory drive at all ventilation-matched work rates. These findings are consistent with the hypothesis that the demands of dynamic UBE are sufficient to compromise the mechanical-ventilatory efficiency of the respiratory system.

4-4.1 Tidal Volume Constraint

Tidal volume was significantly lower during UBE compared to LBE (1.97 ± 0.85 vs. 2.55 ± 0.72 L, at 100% $\dot{V}_{EARM}$) despite exercise modes exhibiting similar $\dot{V}_E$. An unexpected finding was that V_T was also lower at rest prior to UBE and this may be due to a disparity in the resting body position. Resting data prior to UBE were collected while participants sat upright on a chair, in front of the arm-crank ergometer, with hands relaxed at the side. Resting data prior to LBE were collected while participants sat upright on the stationary bike with their hands rested on the upper-handle bars to support the weight of the thorax and prevent slouching. Despite efforts to replicate the resting position between trials, it is likely that greater internal work was performed by participants via thoracic muscle contractions to stiffen the spine (Hodges *et al.*, 2005) and maintain an upright posture on the stationary bike. The larger V_T observed prior to LBE was perhaps initiated to meet an elevated metabolic demand resulting from additional muscle contractions. Oxygen uptake was also minimally higher prior to LBE, but this was not statistically significant. The disparity in resting V_T is insufficient, however, to explain the large differences observed during dynamic UBE and LBE.

The substantial V_T constraint observed during dynamic UBE may be due to several interrelated mechanisms. Upper-body exercise results in greater thoracic muscle work than LBE, and may impose a mechanical limitation on the ribcage. In this study, rectus abdominis EMG was substantially higher during UBE vs. LBE at any given work rate; at peak exercise intensities values were 72.8 ± 62.3 vs. 15.3 ± 7.9% RMS_{MAX}, respectively. The values observed during LBE are in accordance with previous studies in cycling (20 – 40% MVC, Abraham *et al.*, 2002) but there is a paucity of literature making these measurements during dynamic UBE. Since $\dot{V}_E$ was

similar between exercise modes, the greater abdominal muscle activity during UBE likely reflects loading of the abdominals for additional non-respiratory tasks.

Oesophageal pressure (pleural pressure) swings were larger during UBE at all external work rates, reflecting greater respiratory muscle contractile force output. Since ventilation was matched across both modes of exercise, it is likely that the greater indices of neural drive (Poe/P_{IMAX}) were attributable to additional contractions of the thoracic muscles to support posture and arm movement, thereby increasing intra-thoracic pressure swings (Couser *et al.,* 1992). Large pleural, abdominal, and transdiaphragmatic pressure swings are capable of producing substantial distortions and stiffening of the ribcage (Kenyon, Cala, Yan, Aliverti, Scano *et al.*, 1997), and although ribcage distortions are relatively small during cycle ergometry due to coordinated actions of the respiratory muscles (Kenyon *et al.,* 1997), this has not been assessed during arm-cranking. Furthermore, all muscles involved in respiration must attach to the ribcage. Numerous other thoracic muscles with less of a dominant role in breathing also attach to the ribcage, including those required for upper-limb locomotion and trunk stabilisation. Forceful contractions of such muscles likely exacerbate ribcage stiffness with increasing force output from the upper-limbs. This may, in turn, increase chest wall impedance (Criner and Celli, 1988; Takano, 1993; Baarends *et al.*, 1995). A greater relative degree of ribcage stiffness during UBE is likely responsible for $\dot{V}_E$ during UBE commonly being achieved via increases in f_R as opposed to V_T (Takano *et al.,* 1993; Alison *et al.,* 1998; Cerny and Ucer, 2004; Hannink *et al.*, 2010). This reflects present observations at intensities above 80% $\dot{V}_{EARM}$.

Finally, although not characterised in this study, it is possible that additional loading of the respiratory muscles during UBE made them more susceptible to fatigue, which has been repeatedly observed during high-intensity lower- or whole-body exercise (Johnson *et al.,* 1993; Mador *et al.,* 1993; Babcock *et al.,* 1995, 1996, 1998, 2002; Taylor *et al.,* 2006; Verges *et al.,* 2006). Patients being weaned from mechanical ventilation adopt a pattern of rapid, shallow breathing immediately following withdrawal of assisted ventilation (Tobin, Perez and Guenther, 1986). The change in respiratory pattern likely occurs to minimise the work of breathing and move the tension-time index and inspiratory quotient to a region that is less likely to result respiratory muscle fatigue (Milic-Emili, 1986). It is possible, therefore, that the respiratory patterns of UBE, i.e. reduced V_T and increased f_R may be a pre-emptive strategy to 'offload' the respiratory muscles, and thereby minimise the likelihood of impending respiratory muscle fatigue. Further studies on the prevalence of this phenomenon during UBE are required to test this hypothesis.

4-4.2 Operating Lung Volumes and EFL

End-expiratory lung volume was significantly elevated during peak UBE relative to LBE (39 ± 8 vs. 29 ± 8 % FVC). The increase in EELV occurred at ~60% of the maximal $\dot{V}_E$ exhibited during cycling (i.e. 98.5 ± 18.9 $L \cdot min^{-1}$). This is in accordance with Alison *et al*. (1998) who also observed a significantly elevated EELV during arm-cranking compared to leg-cycling when healthy participants exercised at 40 and 60% of peak leg $\dot{V}_E$. EELV during UBE did not rise above baseline and is not, therefore, considered to be dynamic hyperinflation which is strictly defined as an elevation above normal of the resting FRC or EELV (Ferguson, 2006). As such, the rise in EELV can only be expressed relative to that observed during LBE. Any increase in EELV during exercise, however, results in a shortening of the inspiratory muscles (diaphragm, internal obliques, external intercostals) which is deemed mechanically disadvantageous (Alison *et al.*, 1998). Furthermore, increases in EELV exacerbate the work of breathing (Ferguson, 2006) since the inspiratory muscles must overcome additional elastic loads presented by the lung and chest wall (Milici-Emili and Petit, 1960; Alison *et al.*, 1998). High-intensity UBE, therefore, compromises the mechanical efficiency of the respiratory system.

The increase in EELV during UBE at peak intensities was not related to expiratory flow limitation, as is observed in participants with chronic airflow obstruction. These populations increase their operating lung volumes to avoid EFL caused by a partial collapse of the airway under high expiratory pressures (Hannink *et al.*, 2010; Alison *et al.*, 1998; Grimby and Stiksa, 1970; Potter *et al.* 1971; Dodd *et al.* 1984; O'Donnell and Webb, 1993). Dynamic hyperinflation is, therefore, a compensatory mechanism initiated to alleviate limitations to expiratory flow, since ventilating at elevated lung volumes decreases airway resistance and increases elastic recoil to aid expiration (Alison *et al.*, 1998; Porto *et al.*, 2009; Hannink *et al.*, 2010). In this study, once the MEFV envelope had been corrected for the effects of thoracic gas compression and exercise-induced bronchodilation, only two participants experienced EFL during peak UBE (Fig. 4-5). The magnitude of the tidal flow-volume loop that encroached on the MEFV curve was 68 and 81% for the two participants during LBE, and 39 and 52% for the same participants during UBE. The magnitude of EFL was lower during UBE due to a smaller expiratory tidal volume curve. Dynamic airway compression can start at expiratory flow rates ~2 $L \cdot s^{-1}$ below maximal expiratory flow (Mead *et al.*, 1967) and so it may not be necessary for EFL to be present in a healthy cohort for an increase in EELV to occur. Instead, the increase in EELV may occur in reflexive anticipation of reaching the mechanical capacity to generate expiratory flow. Participants in this study, however, did not increase their EELV during LBE at a similar ventilation. Furthermore, most participants exhibited substantial expiratory reserve during UBE. Even when the two flow-

limited participants were removed from the group-mean calculations of EELV, it did not alter the magnitude of the difference between upper- and lower-body exercise. Expiratory flow limitation (or impending EFL) is, therefore, insufficient to explain the elevated EELV in this context.

A more likely explanation relates to the specific motor mechanics of UBE during which respiratory muscles are progressively utilised to stiffen the spine (Hodges *et al.*, 2005) and maintain torso stabilisation and arm position (Celli, 1988). Elevated oesophageal pressures and abdominal muscle activity during arm-cranking, is likely due to increased demands placed on the thoracic muscles for torso stabilisation and rotation of the thorax. Indeed, while the diaphragm makes no significant contribution to trunk rotation (Hudson *et al.*, 2011), it may still play an essential role in posture (van Lunteren *et al.*, 1985), stabilisation of the trunk prior to rapid arm movements (Hodges *et al.*, 1997) and flexion of the upper- and lower-extremities (Kolar *et al.*, 2010). These isometric components may contribute to the elevated Poe observed during UBE. Moreover, the abdominals also have important locomotor functions in flexing and rotating the trunk (Tortora and Grabowski, 2003). There is a direct competition, therefore, for the ventilatory, postural and locomotor functions of the respiratory muscles, which may be more pronounced during UBE. UBE impedes the normal recruitment of the abdominal muscles (Cerny and Ucer, 2004), which may in turn, impede the capacity of the expiratory muscles to reduce EELV below functional residual capacity (Henke *et al.*, 1988).

It is plausible that increased thoracic muscle loading during UBE is responsible for the increased central motor command observed presently. At exercise onset, O_2 demand increases and, accordingly, peripheral afferent feedback mechanisms increase descending neural signals from the respiratory centres to spinal locomotor neurons to increase $\dot{V}_E$ via an appropriate mechanical response. During UBE, an increase in neural drive ($\Delta Poe/P_{IMAX}$ and EMG_{ra}) was followed by a disproportionately low mechanical response (lower V_T). This suggests a degree of neuro-mechanical uncoupling, i.e. an uncoupling of the relationship between neural drive to the respiratory muscles and the resulting thoracic volume displacement. Such a response is more commonly observed in participants with COPD (O'Donnell and Laveneziana, 2007), being chiefly attributable to dynamic hyperinflation-induced volume restriction. In the absence of EFL in this study, neuro-mechanical uncoupling is likely due to thoracic muscle loading leading to elevated neural respiratory drive, combined with UBE-mediated mechanical restrictions on ribcage kinematics. It appears, therefore, that UBE reduces the capacity of the respiratory system to optimally respond to increases in central neural drive. Although the extent of uncoupling is unlikely to induce ventilatory failure in healthy participants, the poor effort/displacement ratio

observed during UBE may lead to the activation of central limbic structures and, therefore, form the basis of distressing respiratory sensations and elevated perceptions of dyspnoea (Mahler & O'Donnell, 2005). This may, in turn, reduce exercise tolerance (ATS, 2012).

4-4.3 Cardiorespiratory Responses at Iso-Ventilations

When matched for ventilation, O_2 uptake and f_C were significantly higher ($p < 0.05$) during LBE vs. UBE. Healthy participants generally exhibit a higher $\dot{V}O_{2peak}$ during LBE (Sawka, 1986), whereas UBE induces higher values for $\dot{V}O_2$ at a given submaximal work rate (Bobbert, 1960; Bevegaard *et al.*, 1966; Vrijens *et al.*, 1975; Toner *et al.*, 1983). In this study, the higher $\dot{V}O_2$ during LBE at any given $\dot{V}_E$ is likely related to the greater volume of active muscle mass recruited for limb locomotion. The absolute volume of active mass plays an important role in the mode-specific O_2 consumption (Bergh *et al.*, 1976), and it is reasonable to suppose that ergometry involving the legs and gluteals will induce greater O_2 demands than that utilising the arms, chest, back and shoulders. It is difficult to ascertain the *actual* volume of muscle mass recruited during arm-cranking because muscles of the back and torso are recruited for both force production and torso stabilisation (Koppo *et al.*, 2002), and so direct comparisons remain problematic.

An additional explanation for the elevated $\dot{V}O_2$ during LBE is a disparity between mode-specific O_2 kinetics, which were likely slower during UBE. The $\dot{V}O_2$ time constant following the start of leg exercise is approximately 15 – 30 s (Koppo *et al.*, 2002). Fast-twitch fibres, however, have a higher O_2 cost and a longer time constant ($\dot{V}O_{2T}$) relative to slow-twitch fibres (Crow and Kushmerick, 1982, Kushmerick *et al.*, 1992). Since the upper-limbs have a greater proportion of fast-twitch fibres compared to the lower-limbs (Susheela and Walton, 1969, Gollnick *et al.*, 1972, Johnson *et al.*, 1973; Turner *et al.*, 1997), UBE most likely compromises the O_2 utilisation adjustment, resulting in slower $\dot{V}O_2$ kinetics. Indeed, there are numerous reports that the $\dot{V}O_2$-on response is longer (slower) for arm-cranking compared to cycling (Koppo *et al.*, 2002, Cerretelli *et al.*, 1977, Casaburi *et al.*, 1992, Koga *et al.*, 2001). Another mechanism that may impact on $\dot{V}O_2$ kinetics during UBE is the lower noradrenaline release (and thus sympathetic drive) associated with UBE. This may, in turn, induce slower phase-II $\dot{V}O_2$ kinetics by delaying O_2 delivery to active muscles during arm exercise (Hughson and Imman, 1986). In the current study, work rate was increased at 4 minute intervals and average O_2 uptake may, therefore, have favoured the faster O_2-on kinetics of LBE.

Ventilatory equivalents for CO_2 ($\dot{V}_E/\dot{V}CO_2$) were higher during UBE with main effects ($p < 0.05$) reflecting previous studies in arm-cranking (Louhevaara *et al.*, 1990; Takano *et al.*, 1993).

Participants in this study exhibited higher f_R at intensities above 60% $\dot{V}_{EARM}$ which, combined with a lower V_T, likely increased the ventilation dead space volume relative to LBE, which induce a degree of alveolar ventilation-perfusion mismatch. Some studies report that arm exercise end-tidal and arterial PCO_2 is 3 - 4 mmHg lower than that reported for leg exercise in the aerobic range (Sawka *et al.*, 1982; Szal and Schoene, 1989) and is attributed to relative hyperventilation. This may account for an increased $\dot{V}_E/\dot{V}CO_2$ ratio towards the end of exercise. Given that $\dot{V}_E/\dot{V}CO_2$ was slightly higher during UBE at the lower work rates, i.e. when f_R was similar between exercise modes, another explanation may relate to the mechanically-imposed reduction in ribcage movement during arm-cranking. Coupled with a relatively increased movement of the diaphragm and abdominal muscles (Celli *et al.*, 1988), such ribcage kinematics might alter the regional differences in the ventilation/perfusion ratio in the lungs, thereby decreasing PCO_2. A sustained disruption in ventilatory efficiency during UBE would also affect arterial saturation rates and yet no differences in SpO_2 were observed at maximal capacities. Further studies are needed to comprehensively assess the influence of UBE on gas exchange efficiency.

4-4.4 Summary

Healthy, able-bodied men exhibit a marked reduction in mechanical-ventilatory efficiency during UBE. At a given ventilation, UBE significantly constrains tidal volume, while simultaneously increasing neural respiratory drive. Furthermore, EELV increases significantly at peak UBE intensities, relative to LBE, in the absence of EFL. These acute responses are related to the mechanical demands of UBE during which the respiratory muscles are progressively recruited for combined ventilatory, postural and locomotor functions. Such mechanical inefficiency may limit the ability of the organism to perform tasks with a heavy dependence on the upper-limbs and, therefore, has important implications for both athletic and clinical populations.

Chapter Five

EFFECT OF CADENCE AND WORK RATE ON RESPIRATORY MECHANICS DURING UPPER-BODY EXERCISE IN HEALTHY HUMANS

ABSTRACT

Introduction: High cadence arm-cranking results in elevated O_2 uptake ($\dot{V}O_2$) and cardiac frequency (f_C) relative to low cadences at a given submaximal work rate. Since arm-cranking at lower cadences increases force output through the crank-shaft, whereas high cadences may exacerbate postural demands, we reasoned that changes in cadence would provide an effective model with which to test the relationship between thoracic muscle loading and mechanical ventilatory responses to upper-body exercise (UBE). **Aim:** To assess the influence of cadence and work rate on respiratory mechanics during arm-crank exercise in healthy participants. **Methods:** Eight healthy, recreationally-active men (24 ± 4 [S.D.] y) performed arm-crank ergometry at moderate (80% of gas exchange threshold) and severe (65% of the difference between gas exchange threshold and $\dot{V}O_{2peak}$) intensities, each separated by 10 min rest. For each work rate, participants exercised for 4 min at three different cadences (50, 70 and 90 rev·min^{-1}), with 4 min passive rest between cadences. While the order of work rates was sequential, the order of cadences was randomised and counterbalanced. Measurements included baseline pulmonary function, cardiorespiratory indices, electromyographic activity of the diaphragm (EMG_{di}) using a multi-pair oesophageal electrode catheter, pressure-derived indices of respiratory mechanics, locomotor-respiratory coupling (LRC) via whole- and half-integer ratios and perceptual responses of the intensity of breathing and limb discomfort (Borg CR10). **Results**: Pulmonary function was within normal limits. At moderate work rates, $\dot{V}O_2$ and f_C were highest at 90 rev·min^{-1} ($p < 0.05$) relative to 70 and 50 rev·min^{-1} ($\dot{V}O_2$ 1.19 ± 0.25 vs. 1.05 ± 0.21 vs. 0.97 ± 0.24 L·min^{-1}; f_C 116 ± 11 vs. 101 ± 13 vs. 101 ± 12 b·min^{-1}). Furthermore, $\dot{V}_E$ was highest at 90 rev·min^{-1} ($p < 0.05$) due primarily to an increase in V_T ($p < 0.05$). At severe work rates, there were no differences in $\dot{V}O_2$, f_C, $\dot{V}_E$ or breathing pattern across cadences. There was a trend towards elevated intra-thoracic pressures at higher cadences, but no differences in EMG_{di} or operating lung volumes across cadences. During moderate intensity exercise, participants most frequently engaged in LRC at 70 vs. 50 rev·min^{-1} (27 ± 10 vs. 13 ± 9%) and during severe exercise at 90 vs. 50 rev·min^{-1} (24 ± 7 vs. 18 ± 5%), and a concomitantly shorter duty cycle and mean inspiratory flow ($p < 0.05$) at high cadences. **Conclusion:** Moderate intensity, high cadence arm-cranking resulted in greater cardiorespiratory stress and intra-thoracic pressures relative to low cadences. The influence of cadence on physiological function is minimal at severe work rates. Greater prevalence of locomotor-respiratory coupling at higher cadences suggests an increased antagonistic loading of the thoracic muscles, likely the result of greater isometric postural work.

5-1 Introduction

During upper-body exercise (UBE), ventilatory demand is met predominantly via increases in respiratory frequency rather than tidal volume (Takano *et al.*, 1993; Alison *et al.*, 1998; Cerny and Ucer, 2004; Hannink *et al.*, 2010). Furthermore, when compared to lower-body exercise (LBE) at a similar ventilation, UBE results in smaller reductions in EELV (Alison *et al.*, 1998). Although an increase in exercise EELV is commonly seen in patients with obstructive lung disease (Hannink *et al.*, 2010; Alison *et al.*, 1998; Grimby and Stiksa, 1970; Potter *et al.*, 1971; Dodd *et al.*, 1984; O'Donnell and Webb, 1993; O'Donnell *et al.*, 2009; Guenette *et al.*, 2012; Chin *et al.*, 2013), these populations increase their operating lung volumes to offset expiratory flow limitation (EFL) which may be predicated by the (partial) collapse of the airways under high intra-thoracic pressures. In Chapter 4, it was reported, however, that healthy participants increase their EELV more during UBE than LBE in the absence of ventilatory constraint. Due to a shortening of the respiratory muscles at end expiration, this breathing strategy may be mechanically disadvantageous and exacerbate the elastic work of breathing (Milici-Emili and Petit, 1960). This, in turn, may contribute to the elevated dyspnoea experienced by healthy participants during UBE compared to LBE (Celli *et al.*, 1985). In addition, in the previous chapter it was reported that arm-cranking increased both respiratory muscle work and expiratory muscle activation compared to ventilation-matched leg-cycling. The absence of EFL in the group of healthy participants means that the increase in EELV observed during peak UBE requires an alternative explanation.

The underlying mechanisms for the respiratory mechanics of UBE may relate to several interrelated phenomena. First, dynamic LBE results in the progressive recruitment of abdominal and accessory expiratory muscles to reduce EELV below relaxation volume (Henke *et al.*, 1988; Dempsey *et al.*, 1993). The reduction in EELV aids in the expansion of V_T during forced expiration. Forceful movements of the arms during UBE, however, require the additional recruitment of thoracic muscles to stiffen the spine (Hodges *et al.*, 2005), stabilise the trunk (Celli, 1988; Hodges *et al.*, 1997), and flex the upper- and lower-extremities (Kolar *et al.*, 2010). Additional loading of the respiratory muscles for multiple functions may, therefore, compromise the control of EELV during exercise and limit the ability of the organism to perform tasks with a heavy dependence on the upper-body.

Second, movement of the upper-limbs results in elevated intra-thoracic pressure swings (Couser *et al.*, 1992), likely due to additional contractions of thoracic muscles for postural and locomotor

functions. Large pleural, abdominal, and transdiaphragmatic pressure swings result in substantial distortions and stiffening of the ribcage (Kenyon *et al.,* 1997), and although ribcage distortions are relatively small during cycle ergometry due to coordinated actions of the respiratory muscles (Kenyon *et al.,* 1997), this has not been assessed in arm-cranking exercise during which there is a greater demand placed upon the thoracic muscles. Furthermore, since most of the respiratory muscles attach to the ribs or associated structures, it is possible that isometric postural contractions of these muscles during UBE lead to a further stiffening of the ribcage. Such locomotor mechanics may contribute to the constraint of V_T (Alison *et al.,* 1998). Although several studies have assessed the intra-thoracic pressure changes during unsupported arm exercise in healthy participants (Celli *et al.,* 1985; Couser *et al.,* 1992; Mackey *et al.,* 1998), none have used arm-cranking as the exercise modality. As a result, the extent to which thoracic muscle recruitment impacts on the respiratory mechanics of healthy participants during repetitive, cyclical UBE remains unclear.

There is evidence to suggest that manipulating the cadence rate during arm-crank exercise may provide an effective model by which to further investigate the respiratory mechanics of UBE, thereby providing insight into the mechanisms that underpin the responses. There are numerous reports that high arm-crank cadences (70 - 90 rev·min^{-1}) result in elevated $\dot{V}O_2$ and $\dot{V}_E$ at a given submaximal power output, when compared to low cadences (50 - 60 rev·min^{-1}) (Sawka *et al.,* 1983; Price and Campbell, 1997; Smith *et al.,* 2001; 2006a; 2006b; Price *et al.,* 2007). It has been proposed that the elevated cardiorespiratory stress at higher cadences may result from greater isometric contractions of the respiratory muscles for stabilisation of the upper-body and/or the influence of locomotor-respiratory coupling (LRC) on respiratory drive (Price *et al.,* 2007). Since the latter is initiated to facilitate airflow during periods of respiratory muscle antagonistic loading (Bramble and Carrier, 2013), LRC may occur more frequently when exercising at higher cadences. It is plausible, therefore, that higher cadences may exacerbate the postural demands placed upon the respiratory muscles, and negatively impact upon mechanical efficiency.

Studies on leg-cycling exercise, by contrast, tend to report an inverse relationship between cadence rate and the effective forces applied to the crank shaft (Sanderson, 1991; Sanderson, Hennig & Black, 2000), i.e. at a given power output, high cadences result in smaller crank forces. This is most likely because less force is required to overcome the inertia of the flywheel during a shorter duty cycle. During arm-cranking, a reduction in cadence lengthens the duty cycle (Price *et al.,* 2007), likely requiring longer and more forceful contractions of the arms, chest and shoulders to rotate the crank. As a result, there is an increase in trunk and shoulder range of motion in an

effort to recruit a greater volume of active muscle mass into the movement (Price *et al.*, 2007). It is for this reason that low cadence arm-cranking results in a shorter exercise time, most likely due to an earlier onset of peripheral muscular fatigue (Smith *et al.*, 2001; 2006; Price *et al.*, 2007). What is unclear, however, is the extent to which low cadence arm-cranking affects respiratory muscle work and/or recruitment, and the subsequent influence on respiratory mechanics.

5-1.1 Aims and Hypotheses

Given the observation that lower cadences increase forces through the crank shaft, and the proposition that higher cadences may exacerbate the postural isometric demands of the respiratory muscles, it is likely that the mechanical demands of arm-cranking and the physiological responses are intrinsically linked. Manipulating the arm-crank cadence may provide insight into the relationship between thoracic muscle recruitment and mechanical-ventilatory responses. This study, therefore, examined the acute effects of cadence rate on the mechanical-ventilatory responses to submaximal arm-cranking exercise in healthy adults. It was reasoned that high cadence arm-cranking would increase cardiorespiratory stress and increase the prevalence of locomotor-respiratory coupling. It was also hypothesised that low cadence arm-cranking would result in a mechanically-mediated constraint of V_T and associated increase in end-expiratory lung volume. A further hypothesis was that there would be greater diaphragm activation at the higher cadences due to greater static postural demands.

5-2 Methods

5-2.1 Participants

Eight healthy, non-smoking, recreationally-active men between the ages of 18 and 35 y volunteered to participate in the study (mean ± S.D. age 24 ± 4 y, stature 1.76 ± 0.05 m, mass 67.4 ± 6.4 kg). All participants were free from cardiorespiratory disease and excluded from the study if they had undergone systematic endurance or strength training in the 4 months prior to the experiment. The study was approved by the institution research ethics committee and participants provided written informed consent. Participants were asked to abstain from exercise for 48 h, alcohol and caffeine for 12 h, and food for 3 h prior to each visit.

5-2.2 Experimental Design

All procedures were completed during three visits to the laboratory, each separated by a minimum of 2 days and no longer than 1 week. Exercise trials were conducted at the same time of day to eliminate any influence of circadian variance. At the first visit, anthropometric data were collected and baseline pulmonary function assessed via spirometry, whole-body plethysmography and lung diffusion (Table 5-1). Furthermore, participants were familiarised with the breathing manoeuvres and perceptual scales used in subsequent visits. At the second visit, participants completed a maximal ramp incremental exercise test on an arm-crank ergometer to determine maximal power output and associated cardiorespiratory responses. The third visit was designed to assess cardiorespiratory responses, respiratory mechanics and respiratory muscle function during constant-power arm-cranking performed at moderate (80% GET) and severe (~65% ΔGET – $\dot{V}O_{2peak}$) work rates across three cadences (50, 70 and 90 rev·min^{-1}).

5-2.3 Baseline Pulmonary Function

Whole-body plethysmography was used to assess the slow components of lung function (TLC, VC, RV) and airway resistance (sRaw$_{,eff}$ & Raw$_{,eff}$). Indices of dynamic pulmonary capacity (FVC, FEV_1, IC, PEF, MEF) were recorded via spirometry. Single-breath carbon monoxide ($D_{L,CO}$) was used to estimate the diffusion capacity of the alveoli. Spirometry, whole-body plethysmography and carbon monoxide rebreathe were carried out according to recommended standards (Miller *et al.*, 2005; Wanger, 2005; Macintyre *et al.*, 2005).

5-2.4 Maximal Ramp Test

Participants completed a maximal ramp, incremental exercise test on an electromagnetically-braked arm-crank ergometer (Angio; Lode, Groningen, The Netherlands), which had been set in

hyperbolic mode and was mounted to a wall. The ergometer was positioned so the scapula-humeral joint and the distal end of the crank pedal were horizontally aligned. Participants were instructed to sit upright, maintain form at all times and keep their feet flat to the floor to prevent bracing. Arm-cranking commenced at a power of 20 W for 3 minutes after which the work rate was increased by 1 W every 4 s (15 $W \cdot min^{-1}$). The ramp protocol enabled the determination of maximal power output (W_{max}) and associated cardiorespiratory indices within 8 – 12 min (Table 5-2). Pulmonary ventilation and gas exchange (Oxycon Pro; Jaeger GmbH, Hoechberg, Germany) and cardiac frequency (Vantage NV; Polar Electro Oy, Kempele, Finland) were continuously assessed. Gas exchange threshold (GET) was identified using multiple parallel methods (Wasserman, 1984; Beaver *et al.*, 1986).

5-2.5 Constant-Power Exercise Test

Participants completed 2 x 12 min bouts of arm-crank exercise separated by 10 min passive rest. The work rate for each bout was calculated using methods described by Lansley, Dimenna, Bailey & Jones, (2011) and equivalent to either 80% of the GET (moderate) or ~65% of the difference between GET and $\dot{V}O_{2peak}$ (severe). The work rate was adjusted to accommodate for the mean lag time of $\dot{V}O_2$ during ramp exercise, assumed to approximate two-thirds of the initial ramp rate (Whipp *et al.*, 1981). Within each 12 min bout, participants exercised at 50, 70 and 90 $rev \cdot min^{-1}$ in 4 min efforts with 4 min of passive rest between each cadence in order to minimise carry-over effects. Participants exercised at moderate and then severe work rates to minimise fatigue, but cadence order was randomised. Continuous measures of cardiac frequency (f_C) were made by telemetry (Vantage NV; Polar Electro Oy), arterial oxygen saturation (SpO_2) via forehead pulse oximetry (OxiMax N-560, Nellcor, Tyco Healthcare, Pleasanton,CA), ventilatory and pulmonary gas exchange via online gas analysis (Oxycon Pro, Jaeger GmbH), electromyographic activity of the diaphragm (EMG_{di}) and oesophageal and gastric pressures via a multi-pair oesophageal electrode catheter (Gaeltec Devices Ltd, Isle of Skye, Scotland). In the penultimate 30 s of each 4 min effort, participants were asked to rate the intensity of their breathing and limb discomfort using Borg's modified CR10 scale (Borg, 1998). The prevalence of locomotor-respiratory coupling in the middle 2 min of each 4 min effort was calculated retrospectively.

5-2.6 Electromyography

Electromyographic recordings from the crural diaphragm (EMG_{di}) were made using a bespoke multipair oesophageal electrode catheter (Gaeltec Devices Ltd) and used as an index of neural respiratory drive (Luo *et al.*, 2008). The catheter comprised a 100 cm silicon shaft (2.7 mm diameter) with 7 platinum electrodes spaced 1 cm apart. The catheter was passed pernasally into

the stomach until the diaphragm produced a positive pressure deflection on inspiration, and repositioned based on the strength of the EMG_{di} recorded simultaneously from different pairs of electrodes (see *General Methods*). Although previous studies have normalised EMG_{di} against the root-mean square (RMS) from a maximal inspiratory mouth pressure manoeuvre (Vera-Garcia *et al.*, 2010), preliminary data suggested that the highest values for EMG_{di} tended to occur during peak dynamic exercise, possibly due to the combined ventilatory and postural demands of the activity. EMG_{di} was, therefore, normalised against the highest single value achieved during the trial. The EMG signals were sampled at 4 KHz and high-pass filtered at 20 Hz. A notch-filter at 50 Hz was applied to minimise power-line and harmonic interference. The ECG artefact was removed from the digital waveform using a custom script procedure.

5-2.7 Respiratory Mechanics and Operating Lung Volumes

Intra-thoracic pressures were expressed as the change (swing) in pressure during a given inspiration. Oesophageal pressure was also expressed as a percentage of the maximal inspiratory pressure (P_{IMAX}). Continuous measurements of oesophageal pressure ($\Delta Poe_{,insp}$) and gastric pressure ($\Delta Pga_{,insp}$) were made using two pressure transducers attached to the multi-pair oesophageal electrode catheter (Gaeltec Devices Ltd). Transdiaphragmatic pressure ($\Delta Pdi_{,insp}$) was obtained through an independent digital channel created from the subtraction of Poe from Pga. Maximal values for intra-thoracic pressures were obtained from the maximal static inspiratory and expiratory pressure manoeuvres performed prior to the constant-power trials in visits three and four. The pressure transducers were calibrated at the extremes of the physiological range prior using an electro-manometer (C9553, JMW, Harlow, UK).

Operating lung volumes were assessed using inspiratory capacity (IC) manoeuvres and expressed relative to TLC. The IC manoeuvres were performed in duplicate at rest and during the final 30 s of each 4 min exercise stage. Verbal encouragement was given to ensure a maximal inspiratory effort was made and to verify that maximal inspiratory efforts were comparable, the peak inspiratory Poe during each manoeuvre was compared to that obtained at rest. The IC manoeuvre exhibiting the greatest drop in Poe was used in the calculations of operating lung volumes. End-expiratory lung volumes were calculated by subtracting IC from TLC, whereas EILV was calculated as the sum of V_T and EELV. Both EELV and EILV were expressed as a percentage of TLC.

5-2.8 Locomotor-Respiratory Coupling

The entrainment ratio was calculated for each participant as the fraction of crank rate (50, 70 or 90 rev·min^{-1}) to mean f_R recorded in the middle portion of a given exercise stage. Locomotion and respiration were considered to be matched when the instantaneous ratio of a 5 s sample was within ± 0.05 of a whole- or half-integer value (Paterson *et al.*, 1986; Paterson *et al.*, 1987; Sporer *et al.*, 2007). The probability of random chance generating a ratio within ± 0.05 of a whole- or half-integer was ~20% (Paterson *et al.*, 1986). The first and last 60 s of each 4 min block of arm-cranking was excluded from the analysis to account for the stabilisation of respiratory pattern at exercise onset and inspiratory capacity manoeuvres, respectively. The incidence of entrainment (%ENT) was calculated as the percentage of the sampled data within each 4 min effort that met these criteria.

5-2.9 Perceptual Responses

In the penultimate 30 s of each 4 min effort, participants were asked to rate the "intensity of breathing discomfort" and the "intensity of limb discomfort" using Borg's modified CR10 scale (Borg, 1998). The end points were anchored such that zero represented "no breathing/limb discomfort" and 10 was "the most severe breathing/limb discomfort you have ever experienced or could imagine experiencing".

5-2.10 Data Capture

Flow, volume, intra-thoracic pressures and diaphragm EMG signals were fed through a signal amplifier (1902, Cambridge Electronic Design, Cambridge, England) and digitised at sampling rates of 150 and 4000 Hz (EMG) using an analogue to digital converter (micro 1401 mkII, Cambridge Electronic Design). The EMG data were filtered (see Electromyography). All data were incorporated into data acquisition software (Spike 2 version 7.00, Cambridge Electronic Design, Cambridge, England) and displayed simultaneously as digital waveforms.

5-2.11 Statistical Analysis

Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc., IBM, Chicago, IL, U.S.A). Differences in cardiorespiratory function (e.g. $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, f_C, V_T), respiratory mechanics (EELV, EILV, EMG_{di}, $\Delta Poe_{,insp}$ $\Delta Pga_{,insp}$ $\Delta Pdi_{,insp}$) and locomotor-respiratory coupling between cadences were assessed using a three-level (50, 70 and 90 rev·min^{-1}) repeated-measures ANOVA. In cases of statistical significance, post-hoc analysis was conducted using least-significant difference pairwise comparisons. Alpha level was set at 0.05 and data expressed as mean ± S.D unless otherwise stated.

5-3 Results

5-3.1 Participants

Participants exhibited healthy pulmonary function within normal limits (Table 5-1).

5-3.2 Peak Physiological Responses

Peak physiological responses to the maximal ramp incremental exercise test are shown in Table 5-2. Peak oxygen consumption was variable among participants (23.8 – 36.2 $ml \cdot kg^{1} \cdot min^{-1}$), reflecting a range of upper-body fitness. Only two participants exhibited a visible plateau in $\dot{V}O_2$ at end exercise. Moreover, the perceived intensity of limb discomfort was higher than that reported for dyspnoea (10.5 ± 0.5 vs. 7.3 ± 2.0).

Table 5-1: Baseline Pulmonary Function

	Absolute	%Predicted
FVC (L)	5.41 ± 0.92	105 ± 13
FEV_1 (L)	4.36 ± 0.45	101 ± 9
FEV_1/FVC (%)	81.5 ± 6.8	89 ± 8
TLC (L)	7.3 ± 1.2	104 ± 11
RV (L)	1.93 ± 0.47	116 ± 26
FRC (L)	3.74 ± 0.96	114 ± 26
IC (L)	3.58 ± 0.62	95 ± 16
PEF ($L \cdot s^{-1}$)	9.4 ± 1.5	94 ± 13
MVV ($L \cdot min^{-1}$)	186 ± 20	108 ± 14
$sRaw_{,eff}$ ($kPa \cdot s \cdot L^{-1}$)	0.77 ± 0.20	66 ± 17
$Raw_{,eff}$ (kPa^{-1})	0.19 ± 0.05	64 ± 18
DL,CO ($mmol \cdot min^{-1} \cdot kPa^{-1}$)	12.1 ± 1.3	102 ± 12
VA (L)	7.13 ± 0.91	103 ± 8
VI (L)	5.58 ± 0.68	103 ± 9

Mean ± S.D. n=8. Predicted values for spirometry and plethysmography from Quanjer *et al.* (1993), MVV from Neder, Andreoni, Lerario & Nery, (1999). FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; IC, inspiratory capacity; PEF, peak expiratory flow; MVV, maximum voluntary ventilation; $sRaw_{,eff}$, specific effective airway resistance; $Raw_{,eff}$, effective airway resistance; $D_{L,CO}$, diffusion capacity for carbon monoxide; VA, alveolar volume; VI, inspiratory volume.

Table 5-2: Peak Physiological Responses to Ramp Incremental Arm-Crank Exercise

	Rest			Peak		
Work Rate (W)		0		118	±	24
$\dot{V}O_2$ ($L \cdot min^{-1}$)	0.30	±	0.24	2.05	±	0.41
$\dot{V}O_2$ ($ml \cdot kg \cdot min^{-1}$)	4.47	±	0.89	30.3	±	4.5
$\dot{V}CO_2$ ($L \cdot min^{-1}$)	0.24	±	0.06	2.64	±	0.48
RER	0.81	±	0.07	1.29	±	0.06
$\dot{V}_E/\dot{V}O_2$	28.0	±	7.0	38.8	±	5.7
$\dot{V}_E/\dot{V}CO_2$	35.3	±	11.0	29.9	±	3.8
P_ECO_2 (mmHg)	27.6	±	3.7	30.3	±	3.8
f_C ($b \cdot min^{-1}$)	61	±	10	169	±	20
$\dot{V}_E$ ($L \cdot min^{-1}$)	8.2	±	1.6	79	±	17
V_T (L)	0.59	±	0.16	2.02	±	0.51
f_R ($br \cdot min^{-1}$)	14.8	±	4.3	40.9	±	8.0
T_I (s)	2.52	±	1.46	0.73	±	0.13
T_E (s)	2.42	±	0.98	0.82	±	0.24
T_{TOT} (s)	4.93	±	2.33	1.55	±	0.33
T_I/T_{TOT} (s)	0.49	±	0.09	0.47	±	0.05
T_E/T_{TOT} (s)	0.51	±	0.09	0.53	±	0.05
V_T/T_I ($L \cdot s^{-1}$)	0.59	±	0.09	2.78	±	0.59
$CR10_{Limb}$		0		10.5	±	0.5
$CR10_{Dyspnoea}$		0		7.3	±	2.0

Mean ± S.D. n=8. $\dot{V}O_2$, O_2 uptake; $\dot{V}CO_2$, CO_2 output; RER, respiratory exchange ratio; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for O_2; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for CO_2; P_ECO_2, partial pressure of mixed expired CO_2; f_C, cardiac frequency; $\dot{V}_E$, minute ventilation; V_T, tidal volume; f_R, respiratory frequency; T_I, inspiratory time; T_E, expiratory time; T_I/T_{TOT}, inspiratory duty cycle; T_E/T_{TOT}, expiratory duty cycle; V_T/T_I, mean inspiratory flow; $CR10_{Limb}$, intensity of limb discomfort; $CR10_{Dyspnoea}$, intensity of breathing discomfort.

5-3.3 Constant-Power Exercise Test

Cardiorespiratory and Perceptual Responses

Cardiorespiratory responses to the constant-power, cadence-varied exercise test are shown in Table 5-2. Mean power output during moderate and severe exercise was 46 ± 11 W (40 ± 13% W_{max}) and 89 ± 12 W (77 ± 18% W_{max}), respectively. During moderate intensity exercise, arm-cranking at higher cadences tended to induce greater cardiorespiratory stress (Fig. 5-2). Arm-cranking at 90 rev·min^{-1} induced significantly higher values for $\dot{V}O_2$ (p = 0.001), $\dot{V}CO_2$ (p < 0.001), f_C (p = 0.003), $\dot{V}_E$ (p = 0.002) and V_T (p = 0.026) compared to 50 rev·min^{-1}. Furthermore, $\dot{V}O_2$ (p = 0.018), $\dot{V}CO_2$ (p = 0.006), f_C (p = 0.005) and $\dot{V}_E$ (p = 0.013) were higher at 90 compared to 70 rev·min^{-1}. A majority of the differences in cardiorespiratory function across cadences were attenuated by severe exercise. Dyspnoea was greatest at 90 rev·min^{-1} compared to 70 rev·min^{-1} (p = 0.021) and 50 rev·min^{-1} (p = 0.045) during moderate exercise. There were no cadence influences on SpO_2 at either exercise intensity.

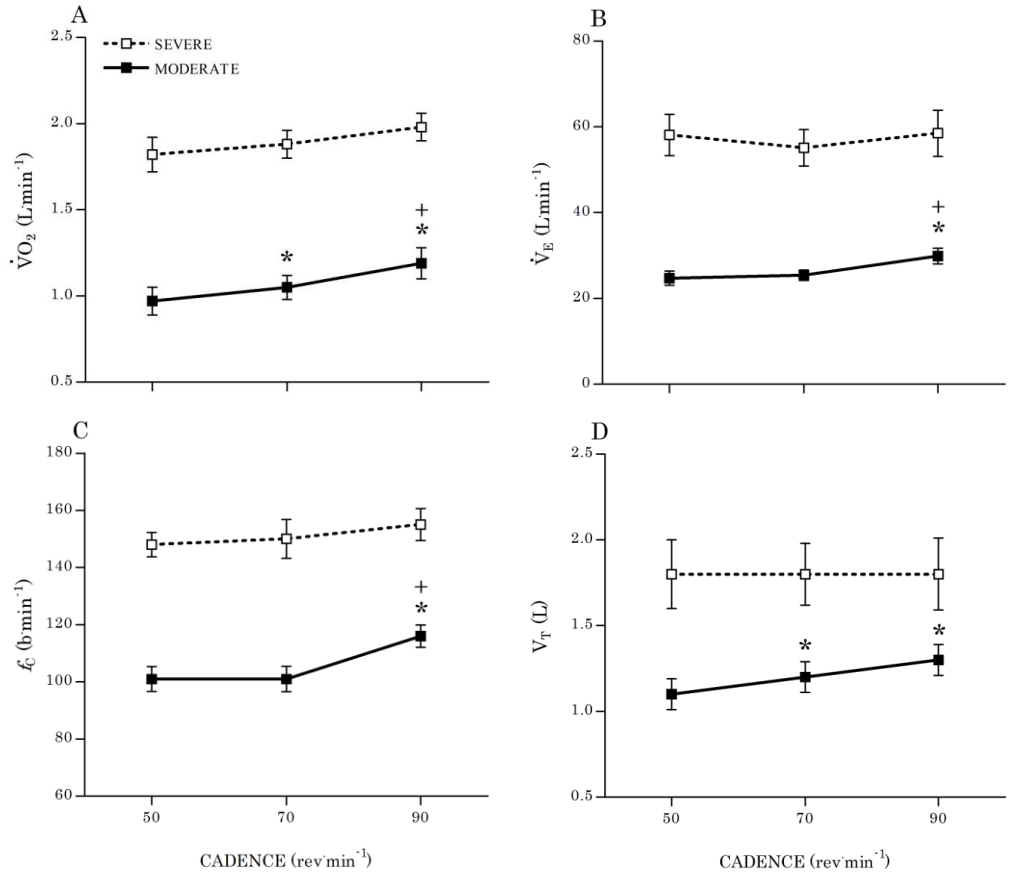

Fig. 5-1: Oxygen uptake (panel A), cardiac frequency (panel B), ventilation (panel C) and tidal volume (panel D) during moderate and severe arm-cranking exercise performed at 50, 70 and 90 rev·min^{-1}. Cardiorespiratory responses at moderate work rates tended to be greater at higher cadences, but the differences were less apparent at the severe work rates. Mean ± S.D. n=8. *Significantly different from 50 rev·min^{-1} ($p < 0.05$); $^{+}$significantly different from 70 rev·min^{-1} ($p < 0.05$).

Table 5-3: Effects of cadence and exercise intensity on cardiorespiratory and perceptual responses during arm-crank exercise

	Moderate			Severe		
	50 rev·min^{-1}	70 rev·min^{-1}	90 rev·min^{-1}	50 rev·min^{-1}	70 rev·min^{-1}	90 rev·min^{-1}
$\dot{V}O_2$ (L·min^{-1})	0.97 ± 0.24	1.05 ± 0.21*	1.19 ± 0.25*$^{+}$	1.82 ± 0.27	1.88 ± 0.23	1.98 ± 0.24
$\dot{V}O_2$ (ml·kg·min^{-1})	14.3 ± 2.9	15.5 ± 2.5*	17.5 ± 2.8*$^{+}$	27.0 ± 2.7	27.9 ± 1.8	29.4 ± 1.4
$\dot{V}CO_2$ (L·min^{-1})	0.94 ± 0.24	1.03 ± 0.24*	1.20 ± 0.26*$^{+}$	1.96 ± 0.31	1.93 ± 0.26	2.03 ± 0.34
RER	0.97 ± 0.11	0.97 ± 0.10	1.00 ± 0.06	1.08 ± 0.09	1.03 ± 0.10	1.02 ± 0.09
$\dot{V}_E/\dot{V}O_2$	26.1 ± 4.0	24.8 ± 4.2	25.5 ± 3.1	31.9 ± 5.9	29.5 ± 6.3	29.3 ± 5.5
$\dot{V}_E/\dot{V}CO_2$	27.2 ± 5.2	25.8 ± 5.6	25.6 ± 3.6	29.5 ± 3.9	28.6 ± 4.9	28.7 ± 4.0
P_ECO_2 (mmHg)	4.15 ± 0.47	4.20 ± 0.38	4.19 ± 0.42	3.59 ± 0.53	3.70 ± 0.62	3.54 ± 0.58
f_C (b·min^{-1})	101 ± 12	101 ± 13	116 ± 11*$^{+}$	148 ± 12	150 ± 19	155 ± 16
$\dot{V}_E$ (L·min^{-1})	24.7 ± 4.7	25.4 ± 3.4	29.9 ± 5.2*$^{+}$	58.1 ± 13.7	55.1 ± 12.0	58.5 ± 15.2
V_T (L)	1.12 ± 0.24	1.23 ± 0.24*	1.28 ± 0.25*	1.82 ± 0.57	1.76 ± 0.51	1.78 ± 0.58
f_R (br·min^{-1})	22.8 ± 4.9	21.3 ± 4.8	24.3 ± 6.5	33.3 ± 7.4	34.0 ± 13.7	35.8 ± 13.2
T_I (s)	1.16 ± 0.18	1.25 ± 0.29	1.02 ± 0.17*$^{+}$	1.52 ± 0.50	1.61 ± 0.65	1.33 ± 0.60^{+}
T_E (s)	1.41 ± 0.28	1.36 ± 0.20	1.39 ± 0.43	0.91 ± 0.26	0.97 ± 0.27	0.84 ± 0.23^{+}
T_{TOT} (s)	2.57 ± 0.44	2.61 ± 0.45	2.40 ± 0.55	2.43 ± 0.62	2.58 ± 0.85	2.17 ± 0.74^{+}
T_I/T_{TOT}	0.45 ± 0.03	0.47 ± 0.04	0.43 ± 0.05	0.62 ± 0.10	0.61 ± 0.08	0.60 ± 0.10
T_E/T_{TOT}	0.55 ± 0.03	0.53 ± 0.04	0.57 ± 0.05	0.38 ± 0.10	0.39 ± 0.08	0.40 ± 0.10
V_T/T_I (L·s^{-1})	1.12 ± 0.15	1.23 ± 0.21	1.28 ± 0.16*$^{+}$	1.25 ± 0.36	1.19 ± 0.40	1.46 ± 0.54
SpO_2 (%)	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 1
$CR10_{Limbs}$	2.3 ± 1.0	2.8 ± 1.1	3.3 ± 1.2	8.3 ± 2.2	7.5 ± 1.7	7.0 ± 2.2
$CR10_{Dyspnoea}$	1.9 ± 1.7	1.7 ± 1.4	2.6 ± 1.4*$^{+}$	5.7 ± 3.1	5.1 ± 2.9	5.4 ± 3.1

Mean ± S.D. n = 8. $\dot{V}O_2$, O_2 uptake; $\dot{V}CO_2$, CO_2 output; RER, respiratory exchange ratio; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for O_2, $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for CO_2; P_ECO_2, partial pressure of mixed expired CO_2; f_C, cardiac frequency; $\dot{V}_E$, minute ventilation; V_T, tidal volume; f_R, respiratory frequency; T_I, inspiratory time; T_E, expiratory time; T_{TOT}, total respiratory time; T_I/T_{TOT}, inspiratory duty cycle; T_E/T_{TOT}, expiratory duty cycle; V_T/T_I, mean inspiratory flow; SpO_2, arterial oxygen saturation; $CR10_{Limbs}$, intensity of limb discomfort; $CR10_{Dyspnoea}$, intensity of breathing discomfort. *Significantly different from 50 rev·min^{-1} ($p < 0.05$); $^{+}$significantly different from 70 rev·min^{-1} ($p < 0.05$).

Respiratory Mechanics and Operating Lung Volumes

Respiratory mechanics during constant-power, cadence-varied tests are shown in Table 5-3. During moderate exercise there was a trend towards greater $\Delta Poe_{,insp}$ (p = 0.081), $\Delta Pdi_{,insp}$ (p = 0.055) and $\Delta Poe/P_{IMAX}$ (p = 0.077) at 90 rev·min^{-1} compared to 50 rev·min^{-1} (see also Fig. 5-2) but the differences were less apparent during severe exercise. The $\Delta Poe/\Delta Pdi$ ratio was not different across work rates or among cadences, suggesting a consistent contribution of the ribcage muscles to transdiaphragmatic pressure generation. EELV was lower during severe compared to moderate exercise, but was mainly accounted for by the larger V_T. There was no effect of cadence on operating lung volumes (Table 5-3). Oesophageal pressure swings during the IC manoeuvres were not significantly different from baseline at any work rate or cadence, suggesting consistent maximal inspiratory efforts. Due to poor digital traces, data for EMG_{di} is presented for n=4. For these participants, diaphragm activity was substantially greater during severe versus moderate exercise (87 ± 18 vs. 32 ± 17% MVC), but not different across cadences (Table 5-3).

Table 5-4: Effects of cadence and exercise intensity on respiratory mechanics during arm-crank exercise

	Moderate			Severe		
	50 rev·min^{-1}	70 rev·min^{-1}	90 rev·min^{-1}	50 rev·min^{-1}	70 rev·min^{-1}	90 rev·min^{-1}
$\Delta Poe_{,insp}$ (cmH_2O)	9.8 ± 3.3	10.9 ± 4.0	12.8 ± 4.5	18.7 ± 7.7	15.7 ± 4.9	16.7 ± 4.4
$\Delta Pga_{,insp}$ (cmH_2O)	11.2 ± 5.4	11.2 ± 3.4	12.2 ± 5.2	22.3 ± 8.8	22.2 ± 8.2	20.3 ± 6.2
$\Delta Pdi_{,insp}$ (cmH_2O)	21.0 ± 7.0	22.0 ± 5.6	25.0 ± 7.9	41.1 ± 12.3	39.2 ± 10.5	37.8 ± 8.4
$\Delta Poe/P_{IMAX}$ (%)	8.5 ± 2.3	9.5 ± 3.4	11.4 ± 4.6	16.2 ± 5.4	14.8 ± 3.7	15.2 ± 3.5
$\Delta Poe/\Delta Pdi$	0.48 ± 0.14	0.49 ± 0.13	0.52 ± 0.12	0.46 ± 0.11	0.44 ± 0.10	0.47 ± 0.09
EILV (%TLC)	73 ± 5	73 ± 3	76 ± 9	81 ± 5	82 ± 8	78 ± 6
EELV (%TLC)	58 ± 6	56 ± 5	59 ± 9	56 ± 8	58 ± 9	53 ± 9
EMG_{di} ($\%_{MAX}$)	34 ± 23	22 ± 7	40 ± 20	89 ± 18	88 ± 17	83 ± 19

Mean ± S.D. n = 8 (EMG, n = 4). $\Delta Poe_{,insp}$, inspiratory oesophageal pressure swing; $\Delta Pga_{,insp}$, inspiratory gastric pressure swing; $\Delta Pdi_{,insp}$, inspiratory transdiaphragmatic pressure swing; $\Delta Poe_{,insp}/P_{IMAX}$, inspiratory oesophageal pressure swing as a percentage of maximum static inspiratory pressure; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; EMG_{di}, electromyographic activity of the diaphragm during inspiration. *Significantly different from 50 rev·min^{-1} ($p < 0.05$); $^{+}$significantly different from 70 rev·min^{-1} ($p < 0.05$).

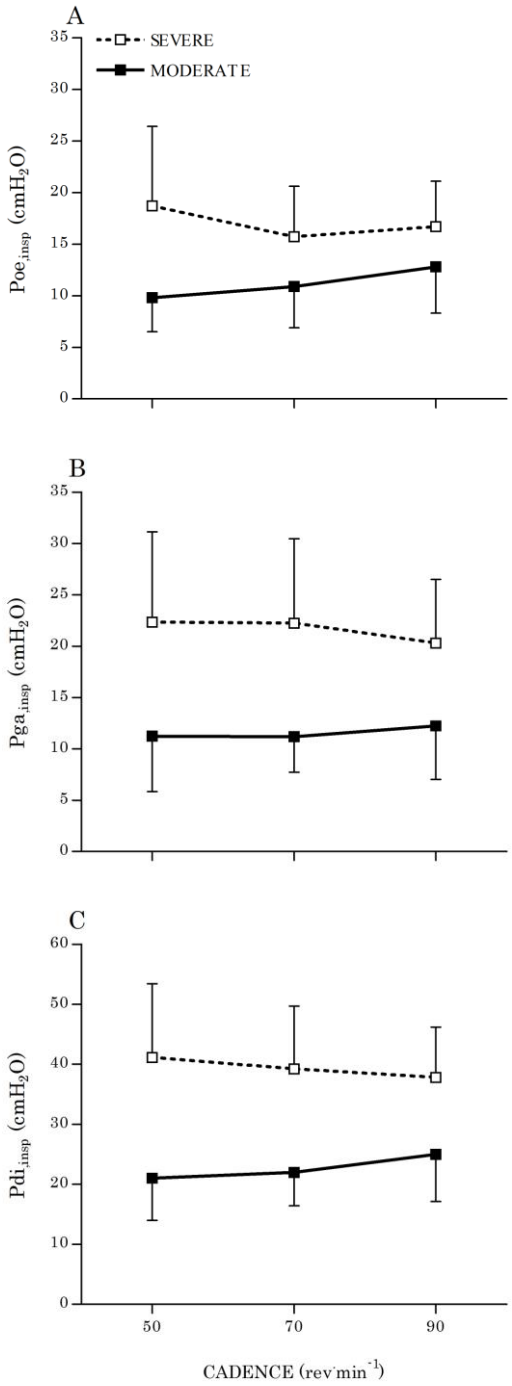

Fig. 5-2: Oesophageal pressure (panel A), gastric pressure (panel B) and transdiaphragmatic pressure (panel C) during moderate and severe arm-cranking exercise performed at 50, 70 and 90 rev·min^{-1}. During moderate exercise there was a trend towards higher Poe, Pga and Pdi at 90 compared to 50 rev·min^{-1}. Mean ± S.D. n = 8.

Locomotor-Respiratory Coupling & Respiratory Duty Cycle

The prevalence of locomotor-respiratory coupling (%ENT) during constant-power, cadence-varied tests are shown in Fig. 5-3. Participants engage in locomotor-respiratory coupling more frequently at the higher cadences. During moderate intensity exercise the prevalence of entrainment at 90, 70 and 50 rev·min^{-1} was in 27 ± 10%, 23 ± 8% and 13 ± 9%, but with no significant differences between 70 and 90 rev·min^{-1}. During severe exercise there was no difference in the frequency of entrainment between 50 and 70 rev·min^{-1}(18 ± 5 and 17 ± 8%, respectively), but entrainment was significantly higher at 90 rev·min^{-1} (24 ± 7%, p = 0.034). At moderate work rates, T_I was shorter at 90 rev·min^{-1} compared to 50 rev·min^{-1} (p = 0.012) and 70 rev·min^{-1} (p = 0.016), and at severe work rates T_I was shorter at 90 rev·min^{-1} compared to 70 rev·min^{-1} (p = 0.049). Mean inspiratory flow was also greater at 90 rev·min^{-1} compared to 70 rev·min^{-1} (p = 0.009) and 50 rev·min^{-1} (p = 0.001) during moderate exercise.

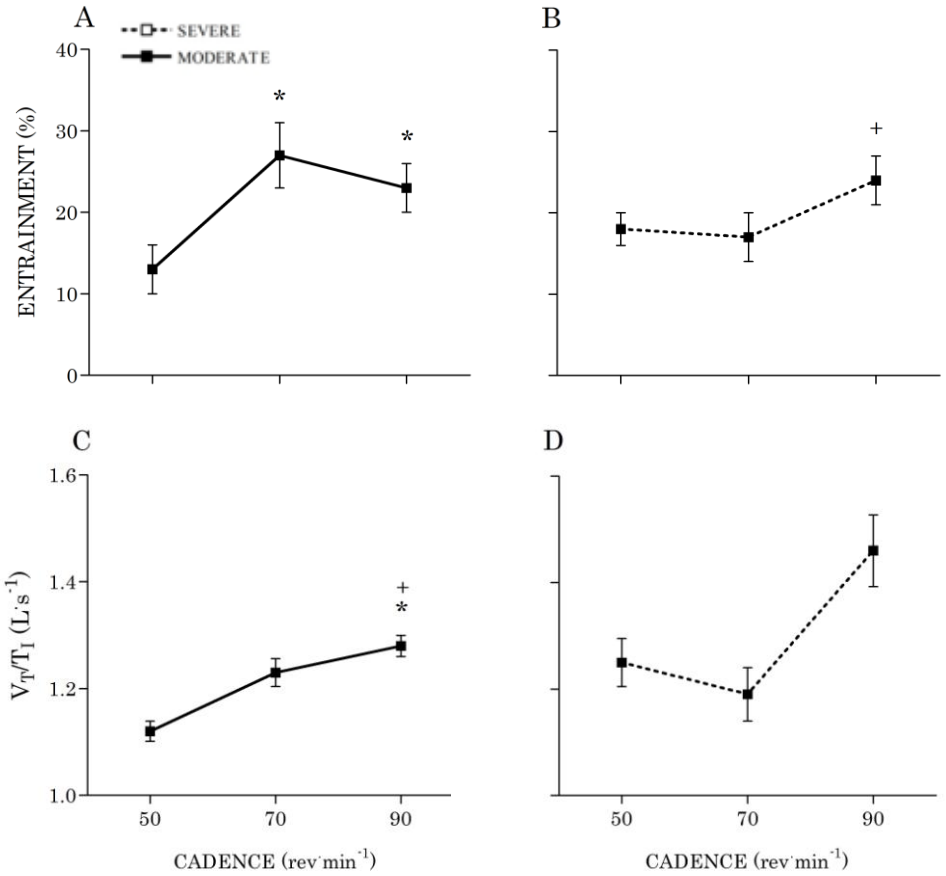

Fig. 5-3: Locomotor-respiratory coupling (entrainment) during moderate (panel A) and severe (panel B) arm-cranking exercise, and mean inspiratory flow during moderate (panel C) and severe (panel D) arm-cranking performed at 50, 70 and 90 rev·min^{-1}. During moderate exercise, the prevalence of entrainment was highest at 70 rev·min^{-1}, and during severe exercise at 90 rev·min^{-1}. Mean inspiratory flow showed a similar cadence influence. ENT, Mean ± S.D.; V_T/T_I, Mean ± S.E.M. n = 8. *Significantly different from 50 rev·min^{-1} ($p < 0.05$); $^{+}$significantly different from 70 rev·min^{-1} ($p < 0.05$).

5-4 Discussion

The aim of this study was to investigate the mechanisms that underpin the respiratory mechanics of UBE. Since low cadences increase forces through the crank shaft, and high cadences may exacerbate the postural isometric demands of the respiratory muscles, we reasoned that manipulating cadence rate during arm-cranking may provide a model with which to assess whether changes in thoracic loading affect breathing patterns and respiratory mechanics. In assessing the acute influence of cadence and work rate on cardiorespiratory function, respiratory mechanics and locomotor-respiratory coupling during arm-cranking, we made several key observations. First, arm-cranking at 90 rev·min^{-1} significantly increased cardiorespiratory stress at moderate work rates when compared to either 50 or 70 rev·min^{-1}. Second, moderate-intensity, high cadence arm-cranking resulted in a trend towards greater intra-thoracic pressures and associated perceptions of dyspnoea, but with no substantial impact on operating lung volumes or diaphragm activation. A third major finding was that participants spent more time engaged in locomotor-respiratory coupling when exercising at higher cadences. These data suggest that for a given submaximal power output, cadence may influence cardiorespiratory function, dyspnoea and respiratory entrainment patterns, as per our primary hypotheses, but not by directly influencing diaphragm activity, which is inconsistent with our secondary hypotheses.

5-4.1 Cardiorespiratory Responses

Participants exhibited significantly higher values for $\dot{V}O_2$, $\dot{V}_E$ and f_C when exercising at higher cadences, despite identical submaximal power outputs. Compared to arm-cranking at 50 rev·min^{-1}, oxygen uptake at 90 rev·min^{-1} was higher during both moderate and severe exercise. Few studies have directly identified the underlying cause(s) of cadence-induced elevations in $\dot{V}O_2$, although several postulations have been put forth.

First, there are reports that both cycling (Sylvester *et al.*, 2011) and arm-cranking (Smith *et al.*, 2006) at low cadences (50 – 60 rev·min^{-1}) significantly increase the magnitude of the $\dot{V}O_2$ slow component when compared to high cadences. Other studies have observed a significant correlation between the time constant of the primary $\dot{V}O_2$ response and the percentage of type-I fibres in the active muscle, i.e. a greater distribution of type-I (slow-twitch) fibres led to faster O_2-on kinetics (Pringle *et al.*, 2003). This is likely associated with a reduced O_2 utilisation adjustment and a longer time constant in type-II fibres compared to type-I (Kushmerick and Crow, 1982; Kushmerick *et al.*, 1992). At a given power output, ergometry performed at low cadences result in an increased duty cycle and, therefore, greater effective forces transferred

through the crank shaft in order to overcome the increased inertia of the flywheel (Sanderson, 1991; Sanderson *et al.*, 2000). Locomotion under such conditions will necessarily require the use of a greater active muscle mass. Since the upper-body is composed of ~50% type-II fibres (Susheela & Walton, 1969; Gollnick *et al.*, 1972; Johnson *et al.*, 1973), it is likely that the additional type-II fibre recruitment negatively impacts on the speed of the O_2-on response. Furthermore, the applied exercise bouts were only 4 min in duration. A reduced O_2 utilisation adjustment, induced by greater fast-twitch fibre recruitment at lower cadences, may have delayed the attainment of steady-state $\dot{V}O_2$.

A second possible cause of the elevated $\dot{V}O_2$ at higher cadences may relate to a disparity in one of several unmeasured work components during arm-cranking, including the transfer of force from skeletal muscles to the ergometer propulsion system, isometric exercises resulting from enhanced postural requirements, and internal work above resting function (Glaser *et al.*, 1984). An increase in any one of these factors induced by high cadence arm-cranking may potentiate an increase in $\dot{V}O_2$ and thereby reduce mechanical efficiency. It is possible that the rapid and repetitive forces transmitted through the upper-limbs and torso during high cadence arm-cranking results in a disruption to the relationship between adjacent spinal vertebrae (Panjabi *et al.*, 1989) and may, therefore, necessitate reactive isometric contractions of various thoracic muscles in order to resist postural disturbances and preserve spinal stability. Since isometric contractions have been shown to elicit the same O_2 uptake per unit of muscle mass as dynamic muscle contractions (Elder *et al.*, 2006), a greater internal isometric work component, resulting from high cadence arm-cranking, may elevate $\dot{V}O_2$ without directly contributing to force output or propulsion of the crank shaft. Although not measured directly in this study, it is likely that the elevated $\dot{V}O_2$ at high cadences resulted in lower values for gross and net efficiency (Sawka *et al.*, 1983; Price and Campbell, 1997; Smith *et al.*, 2001; Smith *et al.*, 2006a; Smith *et al.*, 2006b; Price *et al.*, 2007).

The diaphragm has both inspiratory and static postural functions that are modulated during brief, intermittent arm movements (Hodges *et al.*, 1997; Hodges & Gandevia, 2000). Since the postural disturbances were likely greater during high cadence arm-cranking, it was expected that this would be reflected in greater diaphragm EMG activity, and yet the present data do not support this hypothesis. Although mean diaphragm activity was greater during severe compared to moderate exercise (87% vs. 32% MVC), this may relate to the greater $\dot{V}_E$ at severe work rates. Values for EMG_{di} were similar at 50, 70 and 90 rev·min^{-1} at a given work rate, suggesting that neural drive to the diaphragm was not substantially influenced by cadence rate. There may be several explanations for this. Although diaphragm EMG may increase during static postural contractions

(Hodges *et al.*, 1997l Hodges and Gandevia, 2000), isometric rotational tasks have been shown to leave diaphragm EMG unchanged (Hudson *et al.*, 2010). Furthermore, when $\dot{V}_E$ increases during dynamic exercise, neural input to the diaphragm is altered to prioritise its ventilatory functions (Hodges and Gandevia, 2000), resulting in diminished postural drive. The role of the diaphragm in postural support at higher cadences may, therefore, be minimal. As a result, any exaggeration of isometric postural demands induced by high cadences, may not have been evident during the assessment of diaphragm activity.

Inspiratory drive is distributed differently across different inspiratory muscles, possibly according to their mechanical effectiveness (Butler, 2007). As such, it may be that other trunk muscles contribute more substantially to isometric postural functions. There are increases in EMG activity from the parasternal intercostals during isometric rotational tasks (Hudson *et al.*, 2010) when there is no such activity from the diaphragm. Furthermore, both the rectus abdominis and erector spinae contract phasically during rapid arm movements (Zedka and Prochazka, 1997), but without being modulated when $\dot{V}_E$ increases (Hodges and Gandevia, 2000; Hodges, Heijnen and Gandevia, 2001). Thoracic muscles with less of a dominant role in producing pulmonary ventilation may, therefore, be tasked with maintaining postural stability during high cadence arm-cranking. Further assessment of the accessory respiratory muscles, deep muscles of the abdomen and superficial muscles of the lower back may yield additional insight into their respective postural contributions during dynamic UBE.

Severe Intensity Exercise

During severe exercise, the cadence influences on cardiorespiratory function were diminished, as observed during previous arm-cranking studies (Powers *et al.*, 1984; Smith *et al.*, 2006). The smaller cadence differences in cardiorespiratory function during severe exercise may relate to the greater absolute work rate of severe compared to moderate exercise (77 ± 18% vs. 40 ± 13% W_{max}). It was suggested that unloaded cycling at higher cadences results in a greater energy cost of moving the exercising limbs compared to low cadences (Price *et al.*, 2007). As the power output (and subsequent energy demand) increases, however, the energy cost associated with unloaded cycling becomes an increasingly smaller contributor to total energy expenditure (Price *et al.*, 2007). Moreover, generating a high absolute external power output during severe exercise, likely requires a greater volume of active mass during both high and low cadences, in order to revolve the flywheel. Cardiorespiratory function is ultimately dictated by the greater absolute volume of muscle mass recruited during high intensity arm-cranking, thus minimising the cadence influence on $\dot{V}O_2$ at this work rate.

5-4.2 Locomotor-Respiratory Coupling and Respiratory Duty Cycle

Locomotor-respiratory coupling is a form of breathing entrainment which refers to the phase-locking of locomotor and respiratory frequencies during exercise (Bramble and Carrier, 2013). During dynamic exercise, when loads through the torso exacerbate the mechanical demands of the respiratory muscles, participants may engage in LRC in order to simplify the coordination of respiratory and postural tasks (Hodges *et al.*, 2001). Participants in this study spent a greater proportion of their exercise time engaging in LRC at 70 $rev \cdot min^{-1}$ during moderate exercise, and at 90 $rev \cdot min^{-1}$ during severe exercise. The current data suggest that there is an effect of cadence rate on the prevalence of entrainment during arm-cranking. The present observations reflect that which has gone previously when using integer and half-integer ratios to assess entrainment, i.e. a prevalence of ~25% entrainment during arm-cranking at 90 $rev \cdot min^{-1}$, and a magnitude of entrainment that is independent of workload (Paterson *et al.*, 1986). Furthermore, early studies into breathing entrainment, assessed using cross-correlation to detect relationships between trains of respiratory and locomotor impulses, also observed a greater tendancy to entrain when exercising at faster cadences, although such measurements were made during cycle ergometry (Bechbache & Duffin, 1977).

Phase-locking respiratory and locomotor patterns reduce the mechanical interactions between locomotion and ventilation and may, therefore, minimise the conflict between muscles that contribute to both (Carrier 1991; Deban and Carrier, 2002). Entrainment occurs more frequently, therefore, during periods of heightened respiratory muscle conflict in order to facilitate respiratory flow. This may, in turn, reduce the energy cost of breathing (Daley, Bramble and Carrier, 2013). Although LRC is controlled by both mechanical and neural factors, the primary mechanical factors are thoracic loading and inertial displacement of soft body tissues (Bramble and Carrier, 1983; Bramble and Jenkins, 1993; Lee and Banzett, 1997). Since arm-swinging (during ambulation) has been shown to contribute to compression loads on the thorax (Pontzer, Holloway, Raichlen, Lieberman *et al.*, 2009; Pontzer, Raichlen and Sockol, 2009), the fast, rhythmical rotations of the arms and shoulders under load during arm-cranking likely exacerbate the mechanical interactions between locomotor and ventilatory muscular contractions. The present observation that LRC is more common at 90 $rev \cdot min^{-1}$ during severe exercise is indirect evidence that such conditions result in additional mechanical demands on the thoracic muscles. It is possible that participants more frequently engaged in LRC at faster cadences in order to minimise any impedance to airflow that result from static postural loading during exercise.

There is a strong likelihood that the prevalence of LRC in the present participants resulted from the higher crank rates. When engaged in LRC, healthy participants generally initiate the respiratory cycle to occur during mechanically compatible periods of the locomotor cycle (Daley *et al.,* 2013), i.e. the inspiration to expiration transition is timed to occur at a point in the locomotor cycle which will facilitate, rather than impede, pulmonary airflow. Daley *et al.* (2013) studied LRC during treadmill running and found that the ventilatory transitions that were initiated in mechanically compatible (assistive) phases of the locomotor cycle, occurred twice as fast as those in less compatible phases. The result was a faster inspiration to expiration transition. When the present participants exercised at 90 $rev{\cdot}min^{-1}$ during severe exercise, they exhibited greater values for mean inspiratory flow compared to either 70 or 50 $rev{\cdot}min^{-1}$. Similar patterns were noted for T_I and T_{TOT}, i.e. shorter respiratory cycles at 90 $rev{\cdot}min^{-1}$ during severe exercise. Given that f_R was not different across cadences at either work rate, participants in this study entrained more frequently at higher cadences in order to facilitate V_T expansion via significant increases in respiratory flow. Such respiratory patterns were likely facilitated by the entrainment of the respiratory cycle with assistive phases of the locomotor cycle. The current data regarding the prevalence of LRC is, therefore, consistent with the hypothesis that mechanical-ventilatory function may be further challenged by the postural demands of arm-cranking.

5-4.3 Respiratory Mechanics

Dynamic exercise typically results in changes in intra-thoracic pressures (Thomas *et al.,* 1997) which reflect an increase in the work performed by the respiratory muscles. Intra-thoracic pressures were greater during severe versus moderate exercise, and there was a trend towards elevated $\Delta Poe_{,insp}$, $\Delta Pga_{,insp}$ and $\Delta Pdi_{,insp}$ at the higher cadences during moderate exercise, but not during severe exercise. Since LRC was more frequent at the higher cadences, it is possible that the elevated postural demands of high cadence arm-cranking caused greater respiratory muscle 'work' and, therefore, elevated intra-thoracic pressures. Afferents from the intercostal muscles project to the cerebral cortex and contribute to proprioception (Gandevia & Macefield, 1989), thereby increasing descending neural signals (neural drive) from the respiratory centres to spinal locomotor neurons (Forster, Haouzi & Dempsey, 2012). The result is elevated intra-thoracic pressures that were likely due, at least in part, to mechanical loading of the thorax. A consequence of elevated neural respiratory drive is increased sensory respiratory effort (ATS, 1999). Accordingly, significantly greater perceptions of dyspnoea were observed in participants at the higher cadences. This, in turn, may have implications for exercise tolerance in healthy participants during UBE.

In the previous chapter, dynamic changes in EELV were observed during peak UBE relative to LBE at a similar $\dot{V}_E$. The response was attributed to the exacerbated postural demands placed on the expiratory muscles by UBE, resulting in a relative inability to control EELV. In the present study, it is thought that high cadence arm-cranking may exacerbate disturbances to spinal stability, thus increasing the static postural requirements of the respiratory muscles. It is surprising, therefore, that operating lung volumes were adequately maintained across cadences. The lack of cadence effect on the control of EELV may be due to the short duration of the exercise bouts in this study (4 min) which affected the magnitude of the recorded $\dot{V}_E$. The previously observed increase in EELV occurred in the final 30 s of a maximal incremental arm-crank exercise test, the duration of which was 20 min, and which induced a $\dot{V}_{Epeak}$ of ~99 $L \cdot min^{-1}$. By contrast, participants in this study exercised in 4 min, steady-state bouts, interspersed by 4 min passive rest, inducing a mean $\dot{V}_E$ of ~59 $L \cdot min^{-1}$ during severe exercise. The control of the expiratory muscles over EELV is likely, therefore, to be hyperpnoea-dependent, i.e. the influence of expiratory muscle loading on the control of EELV during arm-cranking may be more apparent at peak arm-cranking ventilations, when V_T is reduced and f_R increased. Although there is a rapid (phase-I) rise in $\dot{V}_E$ at the onset of submaximal exercise, $\dot{V}_E$ continues to rise to a plateau after ~5 min, and may not plateau at all during maximal exercise (Brooks *et al.,* 2004). As such, the exercise bouts used in this study were likely of insufficient duration to induce an appropriate level of cumulative thoracic muscle loading and/or ventilatory drift during which a cadence-induced change in EELV would occur.

An additional explanation for the lack of cadence effect on operating lung volumes, may be that participants chose to 'unload' the expiratory muscles at low cadences through a conscious change in locomotor muscle recruitment. Indeed, during arm-cranking, participants spontaneously adopt crank strategies, i.e. higher cadences, that will most effectively offset localised peripheral muscle fatigue (Weissland *et al.,* 1997; Dekerle *et al.,* 2002; Smith *et al.,* 2007). When a low, fixed crank frequency is imposed as in the present study, it is possible that participants altered their locomotor mechanics in order to recruit greater muscles of the arms chest and shoulders to overcome the increased inertia of the flywheel, while concurrently omitting the major expiratory from involvement in dynamic locomotor contractions. Such a crank strategy would prevent ribcage stiffening and, therefore, preserve respiratory airflow and comfort, even at the expense of potential peripheral muscle fatigue. This hypothesis is consistent with the shorter exercise times, lower peak $\dot{V}O_2$, and greater limb discomfort reported during arm-cranking at lower cadences (Smith *et al.,* 2001; 2006). Adopting such a crank strategy would also minimise the mechanical

constraints on the ribcage during low cadence arm-cranking, resulting in less need to entrain the respiratory and locomotor patterns.

5-4.4 Summary

Higher cadence arm-cranking induced greater cardiorespiratory stress, possibly due to faster O_2-on kinetics and increased isometric postural contractions of the thoracic muscles. At moderate work rates, high cadence ergometry induced greater pressure-derived indices of neural drive and associated perceptions of dyspnoea, but these were not different at severe work rates. Greater locomotor-respiratory coupling at the higher cadences support the hypothesis that high cadence arm-cranking results in greater disturbances to spinal stability resulting in reactive postural contractions; LRC is thus initiated to preserve respiratory airflow. These data suggest that the exacerbated postural requirements of UBE may have an influence on respiratory patterns, cardiorespiratory responses and perceptions of dyspnoea which may have important implications for exercise tolerance during UBE.

Chapter Six

RESPIRATORY MUSCLE FATIGUE IN RESPONSE TO UPPER-BODY EXERCISE IN HEALTHY HUMANS

ABSTRACT

Introduction: Respiratory muscle fatigue occurs frequently following high-intensity whole-body exercise (≥ 90% maximum O_2 uptake), and is associated with a high ventilatory demand. Although upper-body exercise (UBE) induces only submaximal cardiorespiratory stress, it was hypothesised that the additional postural and mechanical loads imposed on the thoracic muscles during UBE, may be sufficient to induce contractile fatigue of the respiratory muscles. **Aim:** To objectively assess the fatigability of the diaphragm and rectus abdominis muscles following arm-cranking performed at heavy and severe work rates. **Methods:** Eight healthy, recreationally-active men (24 ± 4 [S.D.] y) performed constant-power arm-crank exercise at heavy (30% of the difference between gas exchange threshold and $\dot{V}O_{2peak}$) and severe (60% of the difference between gas exchange threshold and $\dot{V}O_{2peak}$) intensities, on separate days and in random order. Measurements included baseline pulmonary function, cardiorespiratory responses, electromyographic activity of the diaphragm (EMG_{di}) and rectus abdominis (EMG_{ra}), pressure-derived indices of respiratory mechanics, pre- and post-exercise blood lactate concentration and perceptual ratings of the intensity of breathing and limb discomfort (Borg CR10). Neuromuscular function was assessed by measuring the transdiaphragmatic twitch pressure ($P_{di,tw}$) and gastric twitch pressure ($P_{ga,tw}$) responses to magnetic stimulation of the cervical and thoracic nerves, respectively, at baseline and at 5 – 15 and 25 – 35 min post-exercise. **Results:** Pulmonary function was within normal limits. Severe arm-cranking exercise induced significantly higher peak $\dot{V}O_2$ ($p < 0.01$), $\dot{V}_E$ ($p < 0.05$), V_T/T_I ($p < 0.01$), [BLa] ($p < 0.01$), EELV ($p < 0.05$), intra-thoracic pressures ($p < 0.01$), W_b ($p < 0.05$), EMG_{ab} ($p < 0.01$) in addition to perceptual ratings of breathing and limb discomfort ($p < 0.05$). There was objective evidence of abdominal muscle contractile fatigue in response to severe- but not heavy-intensity UBE. Specifically, 6 of 7 participants exhibited >10% reduction in $P_{ga,tw}$ with a mean reduction of -22 ± 18% at 5 – 15 min post-exercise. Values had partially returned to baseline at 25 - 35 min (15 ± 15%). There was limited evidence of diaphragm fatigue at both exercise intensities. **Conclusion:** Arm-cranking is of insufficient ventilatory stress to induce contractile fatigue of the diaphragm in healthy, able-bodied participants, but causes expiratory muscle fatigue through a combination of mechanical, postural and ventilatory stress. These novel findings have important implications for athletes competing in upper-body dependent sports, in addition to those with cardiorespiratory disease who participate in UBE training or pulmonary rehabilitation programmes.

6-1 Introduction

Respiratory muscle fatigue occurs frequently following high-intensity whole-body exercise (≥ 90% maximum O_2 uptake) sustained to the limit of tolerance (Johnson *et al.,* 1993; Mador *et al.,* 1993; Babcock *et al.,* 1995, 1996, 1998, 2002; Taylor *et al.,* 2006; Verges *et al.,* 2006). Furthermore, a majority of studies assessing this phenomenon have done so objectively using electromagnetic nerve stimulation techniques (Janssens *et al.,* 2013). Since diaphragm fatigue is thought to be associated with high ventilatory demand and competition for cardiac output at high exercise intensities (Romer & Polkey, 2008), most studies have assessed respiratory muscle fatigue in response to cycle ergometry or treadmill running, i.e. exercise modalities most likely to induce a maximal cardiorespiratory stress. Indeed, peak ventilation rates during exercise in the aforementioned studies have reached 120 - 150 $L \cdot min^{-1}$.

Maximum intensity upper-body exercise (UBE) represents only a submaximal cardiopulmonary stress when compared against values achieved during maximum lower-body exercise (LBE, Vokac *et al.,* 1975; Bergh *et al.,* 1976; Cerretelli *et al.,*1977; Seals and Mullin, 1982; Sawka *et al.,* 1982; Martin *et al.,* 1991). This is due, principally, to the lower active skeletal muscle mass involved in locomotion. Several of the respiratory muscles, however, including the diaphragm and rectus abdominis, have important functions in the maintenance of posture during upper-limb tasks; these include stiffening the spine (Hodges *et al.,* 2005) and maintaining torso stabilisation and arm position (Celli, 1988). Specifically, the diaphragm aids in trunk stabilisation prior to rapid arm movements (Hodges *et al.,* 1997) while the abdominal muscles contract dynamically to flex and rotate the trunk (Tortora and Grabowski, 2003). Given the combined postural, ventilatory and locomotor functions of the respiratory muscles, it is likely that UBE induces greater contractile work of the diaphragm and abdominals relative to LBE. Additional loading of these muscles for non-respiratory tasks, may make them particularly susceptible to contractile fatigue following UBE, and yet this has not been investigated.

Healthy, able-bodied men exhibit a marked reduction in mechanical-ventilatory efficiency during UBE. At a given ventilation, UBE significantly constrains tidal volume (Takano *et al.,* 1993; Alison *et al.,* 1998; Cerny and Ucer, 2004; Hannink *et al*., 2010) compared to LBE. Furthermore, peak UBE significantly elevates EELV relative to LBE, in the absence of EFL (Alison *et al.,* 1998), and disrupts the causal relationship between neural respiratory drive and ventilatory output (Chapter 4). As such, although the abdominals are tasked with reducing EELV during forced expiration (Dempsey *et al.,* 1993) in order to maintain mechanical efficiency, the antagonistic loading of the expiratory muscles during dynamic UBE, appears sufficient to compromise the

effective control of EELV. This enforced breathing strategy, shortens the inspiratory muscles and increases the elastic work of breathing by reducing respiratory compliance. Since the metabolic and circulatory costs of a high work of breathing can contribute ~ 10% of the $\dot{V}O_{2max}$ in untrained participants (Aaron, Johnson, Seow & Dempsey, 1992), and ~ 16% $\dot{V}O_{2max}$ in trained participants (Harms *et al*., 1998), such UBE-induced respiratory mechanics can negatively impact exercise tolerance in patients and athletes alike.

There is also evidence to suggest that the magnitude of respiratory muscle fatigue following exercise may be intensity-dependent, i.e. there may be a causal relationship between the amount of work performed by the respiratory muscles and the magnitude of fatigue. Following high-intensity cycling, the incidence and magnitude of diaphragm fatigue was reportedly greater in participants who exercised at intensities in excess of 85% $\dot{V}O_{2max}$ (Johnson *et al.,* 1993). Furthermore, the magnitude of contractile fatigue measured post-exercise, was significantly correlated with both the magnitude of work performed by the diaphragm and relative $\dot{V}O_2$ at end exercise (Johnson *et al.,* 1993). By contrast, Verges *et al.* (2006) report no such correlations between absolute or relative $\dot{V}O_2$ and the magnitude of expiratory muscle fatigue. There was also no relationship between the reduction in $P_{ga,tw}$ following exercise and the ventilatory output or work performed by the abdominal muscles, observations also reported by Taylor *et al.* (2006). As such, the notion that the magnitude of respiratory muscle fatigue may be fitness or intensity-dependent is somewhat contentious. In the aforementioned studies of lower-body exercise, the 'work' measured was principally comprised of the work performed by the respiratory muscles in producing exercise hyperpnoea, and not the additional mechanical demands that may be imposed by UBE. An important, as of yet undetermined component of respiratory muscle fatigue, is the cumulative force output of the respiratory muscles resulting from the combined ventilatory, postural and locomotor functions induced by dynamic upper-limb exercise.

6-1.1 Aims and Hypotheses

In light of the aforementioned considerations, this study used magnetic stimulation of the cervical and thoracic nerve roots to assess the fatigability of the diaphragm and rectus abdominis muscles following arm-cranking performed at heavy and severe work rates. It was hypothesised that, despite inducing only submaximal cardiorespiratory stress, high intensity arm-cranking would be sufficient to induce contractile fatigue of the respiratory muscles due to the combined ventilatory, postural and locomotor demands of the exercise. Furthermore, it was expected that the incidence and magnitude of contractile fatigue would be greater following exercise at a higher external work rate.

6-2 Methods

6-2.1 Participants

Eight healthy, non-smoking, recreationally-active men between the ages of 18 and 35 y volunteered to participate in the study (mean ± S.D. age 24 ± 4 y, stature 1.8 ± 5.5 m, mass 75.5 ± 6.3 kg). All participants were free from cardiorespiratory disease, and were excluded from the study if they had undergone systematic endurance or strength training in the 4 months prior to the experiment. The nature of the study and associated testing protocols were explained, but participants were not informed of the study hypotheses. The study was approved by the institution research ethics committee and participants provided written informed consent. Participants were asked to abstain from exercise for 48 h, alcohol and caffeine for 12 h, and food for 3 h prior to each test.

6-2.2 Experimental Design

All procedures were completed during four visits to the laboratory, each separated by a minimum of 2 days and no longer than 1 week. Exercise trials were conducted at the same time of day to eliminate any influence of circadian variance. At the first visit, anthropometric data were collected and baseline pulmonary function assessed via spirometry, whole-body plethysmography and lung diffusion (Table 6-1). Furthermore, participants were familiarised with the maximal breathing manoeuvres and magnetic stimulation protocols used in subsequent visits. At the second visit, participants completed a maximal ramp incremental exercise test on an arm-crank ergometer to determine maximal power output and associated cardiorespiratory responses. The third and fourth visits were designed to assess cardiorespiratory function, respiratory mechanics and neuromuscular function during two independent constant-power exercise tests performed to the limit of tolerance at heavy and severe intensities. Objective measures of diaphragm and abdominal muscle contractile function were made before and after exercise. The ergometer was set in 'hyperbolic' mode and cadence was standardised at 75 rpm.

6-2.3 Baseline Pulmonary Function

Whole-body plethysmography was used to assess the slow components of lung function (TLC, VC, RV) and airway resistance (s*R*aw,eff and *R*aw,eff). Maximal indices of lung capacity (FVC, FEV_1, IC, PEF, MVV) were recorded via standard spirometry. Single-breath carbon monoxide ($D_{L,CO}$) was used to estimate the diffusion capacity of the alveoli. Maximal inspiratory and expiratory mouth pressures (MIP and MEP) were assessed at the start of visits 3 & 4 using a handheld pressure meter. Spirometry, whole-body plethysmography, carbon monoxide rebreathe

and maximal inspiratory and expiratory pressures were carried out according to recommended standards (Miller *et al.,* 2005; Wanger, 2005; Macintyre *et al.,* 2005).

6-2.4 Maximal Ramp Test

Participants completed a maximal ramp incremental exercise test on an electronically-braked arm-crank ergometer (Angio; Lode, Groningen, The Netherlands) which was mounted to the wall of the laboratory and positioned so the scapula-humeral joint and the distal end of the crank pedal were horizontally aligned. Participants were instructed to sit upright, maintain form at all times and keep their feet flat to the floor to minimise bracing. Arm ergometry commenced at a power of 20 W for 3 min after which the work rate was increased by 15 $W \cdot min^{-1}$. The ramp protocol allowed the determination of maximal power output (W_{max}) and associated cardiorespiratory indices within 8 – 12 min. Pulmonary ventilation and gas exchange (Oxycon Pro, Erich Jaeger GmbH, Hoechberg, Germany) and cardiac frequency (Vantage NV; Polar Electro Oy, Kempele, Finland) were continuously assessed. Subjective gas exchange threshold (GET) was then identified using multiple parallel methods (Wasserman, 1984; Beaver *et al.,* 1986).

6-2.5 Constant-Power Exercise

Following 3 min of resting tidal breathing, arm ergometry commenced at 20 W for 3 min after which the power was increased instantaneously to a work rate that was equivalent to either 30% or 60% of the difference between GET and $\dot{V}O_{2peak}$; this corresponded to heavy (Δ30%) and severe (Δ60%) exercise, respectively (Lansley *et al.,* 2011). The calculated work rate was adjusted to accommodate for the mean lag time of $\dot{V}O_2$ that occurs during ramp exercise, assumed to approximate two-thirds of the initial ramp rate, i.e. 15 $W \cdot min^{-1}$ (Whipp *et al.,* 1981). Participants were required to exercise to the limit of tolerance but were stopped during heavy exercise if the exercise time exceeded 30 min. The order of trials was randomised and counterbalanced. Continuous measures of cardiac frequency (f_C) were made by telemetry (Polar Vantage NV; Polar Electro Oy), arterial oxygen saturation (SpO_2) by forehead pulse oximetry (OxiMax N-560, Nellcor, Tyco Healthcare, Pleasanton,CA), and ventilation and pulmonary gas exchange via online gas analysis (Oxycon Pro, Erich Jaeger GmbH, Hoechberg, Germany). Neuromuscular activation (electromyogram, EMG) of the diaphragm (EMG_{di}) and rectus abdominis (EMG_{ra}) muscles was assessed using a multi-pair oesophageal electrode catheter (Gaeltec Devices Ltd, Isle of Skye, Scotland) and skin surface electrodes (Trigno Lab, Delsys Inc, Natick, Massachusetts), respectively. Oesophageal and gastric pressure indices were measured via two independent pressure transducers attached to the catheter, positioned proximally and distally to the electrodes. Blood lactate concentration was measured at rest and immediately post-

exercise via 10 µl earlobe capillary sample (Biosen C-Line, EKF Diagnostic GmbH, Barleben, Germany). Perceptual measures of dyspnoea were made using the Borg CR10 scale (Borg, 1998) and inspiratory capacity manoeuvres were performed to assess operating lung volumes. Perceptual measures started at the first minute and IC manoeuvres at the second minute, with both measures continuing thereafter on alternate minutes. The intensity of breathing and limb discomfort (Borg CR10) were made retrospectively at the cessation of exercise. Objective measures of diaphragm and abdominal muscle contractile function were assessed before and after exercise by measuring the change in transdiaphragmatic twitch pressure ($P_{di,tw}$) and gastric twitch pressure ($P_{ga,tw}$), respectively, in response to magnetic stimulation of the relevant spinal nerve roots (see below).

6-2.6 Electromyography

Inspiratory muscles

Recordings from the crural diaphragm were made using a multi-pair oesophageal electrode catheter (Gaeltec Devices Ltd) and used as an index of neural respiratory drive (Luo *et al.*, 2008). The catheter comprised a 100 cm silicon shaft (2.7 mm diameter) with 7 platinum electrodes spaced 1 cm apart. The catheter was passed pernasally into the stomach until the diaphragm produced a positive pressure deflection on inspiration, and re-positioned based on the strength of the EMG_{di} recorded simultaneously from different pairs of electrodes. Although previous studies have normalised EMG_{di} against RMS from a maximal inspiratory mouth pressure manoeuvre (Vera-Garcia *et al.*, 2010), preliminary studies indicated that the highest values for EMG_{di} tended to occur during peak dynamic exercise, possibly due to the combined ventilatory and postural demands of the activity. EMG_{di} was normalised, therefore, against the highest single value achieved during the trial, whether from an MIP manoeuvre or dynamic exercise.

Expiratory muscles

Recordings from the superficial rectus abdominis were made using a pair of wireless surface electrodes (Trigno Lab, Delsys Inc) positioned on the main belly of the muscle, 2 cm superior and 2 - 4 cm lateral to the umbilicus on the right-hand side of the torso. Electrodes were placed in the same orientation as the muscle fibres, i.e. inferolaterally, approximately 8° to the midline (Ng *et al.*, 1998) and secured to the skin using surgical dressing (Tegaderm Dressing, 3M, St. Paul, Minnesota). The RMS of the wave amplitude signal was normalised against the highest single value achieved during the trial, as described previously.

Both inspiratory and expiratory EMG signals were sampled at 4 KHz and high-pass filtered at 20 Hz. A notch-filter at 50 Hz was applied to the diaphragm recording. Since a notch filter is commonly used for suppressing power line and harmonic interference that contaminates the EMG signal (Li, Rymer, Li & Zhou, 2011), this was not deemed necessary for the abdominal muscle recordings that were made using a wireless recording device. The ECG artefact was removed from the digital waveform using a custom script procedure (see *General Methods*).

6-2.7 Respiratory Mechanics and Operating Lung Volumes

Continuous measures were made of the inspiratory change (swing) in oesophageal pressure ($\Delta Poe_{,insp}$) and gastric pressure ($\Delta Pga_{,insp}$). Transdiaphragmatic pressure ($\Delta Pdi_{,insp}$) was obtained through an independent digital channel created from the subtraction of Poe from Pga. Maximal values for intra-thoracic pressures were obtained from maximal static inspiratory and expiratory pressure manoeuvres that were performed prior to the constant-power trials in visits three and four. The work of breathing (W_b) was calculated as the integral of the tidal oesophageal pressure-volume loop multiplied by the respiratory frequency (f_R) (Peters, 1969). The pressure transducers were calibrated at the extremes of the physiological range using an electro-manometer (Mercury M14m Glasgow, Scotland).

Operating lung volumes during exercise were assessed using IC manoeuvres that were expressed relative to TLC. IC manoeuvres were performed in duplicate at rest and during exercise in the final 30 s of alternate minutes starting at the second minute. Verbal encouragement was given to ensure a maximal inspiratory effort was made. To verify that maximal inspiratory efforts were comparable, the peak inspiratory Poe during each manoeuvre was compared to that obtained at rest and between trials. The IC manoeuvre exhibiting the greatest drop in Poe was used in the calculations of operating lung volumes. End-expiratory lung volumes were calculated by subtracting IC from TLC, whereas EILV was calculated as the sum of V_T and EELV. Both EELV and EILV were expressed as a percentage of TLC.

6-2.8 Nerve Stimulation

A monophasic magnetic stimulator (Magstim 200, The Magstim Company Ltd., Whitland, Wales) was used to deliver magnetic stimuli to the spinal foramina that innervated the respiratory muscles. A circular 90 mm coil was positioned at the cervical or thoracic spinal nerve roots to discriminate between the diaphragm and abdominal muscles, respectively, and activated at 100% power when subjects were rested at FRC. Cervical stimulation was favoured over anterolateral stimulation of the phrenic nerves as it allowed the co-stimulation of the diaphragm and ribcage

muscles (Similowski, Straus, Attali, Duguet & Derenne, 1998). This made it possible to independently assess contractile fatigue of the diaphragm and ribcage muscles. To stimulate the inspiratory muscles, participants were required to sit upright with the neck flexed and the coil positioned between the midline of the 5th (C5) and 7th (C7) cervical vertebrae (Similowski *et al.,* 1989). For the expiratory muscles, participants sat facing an inclined bench (~70° from horizontal) with their chest supported, abdomen relaxed and the coil positioned between the 8th (T8) and 11th (T11) thoracic vertebrae (Taylor *et al.,* 2006). In both instances, the optimal coil position was defined as the vertebral level that when stimulated evoked the highest $P_{di,tw}$ (inspiratory) and $P_{ga,tw}$ (expiratory).

6-2.9 Supramaximal Stimulation

To determine whether the respiratory muscles were maximally activated following the delivery of magnetic stimuli, three single twitch manoeuvres were applied to the cervical or thoracic regions at pre-determined percentages of the maximal stimulator output, in an incremental fashion, i.e. 50, 60, 70, 80, 85, 90, 95 and 100%. Each twitch was separated by ~30 s to avoid twitch potentiation. A plateau in mean values of twitch transdiaphragmatic pressure ($P_{di,tw}$) and twitch gastric pressure ($P_{ga,tw}$) would suggest maximal activation of the inspiratory and expiratory muscles, respectively. Supramaximality measures were made ~30 min prior to the constant-power exercise trials and were performed in a randomised and counterbalanced order with the reproducibility trial.

6-2.10 Reproducibility

Diaphragm and abdominal muscle contractile function was assessed before and after 30 min of quiet breathing to determine the within-day, between-trial reproducibility of the nerve stimulation techniques. These reproducibility measures were collected ~30 min prior to the constant-power exercise trials and were performed in a randomised and counterbalanced order with the supramaximality trial.

6-2.11 Respiratory Muscle Fatigue

Neuromuscular function of the inspiratory and expiratory muscles was assessed at baseline and 5 - 15 and 25 - 35 min post-exercise using magnetic stimuli to induce motor-evoked potentials of the spinal nerve roots innervating the relevant muscles. All stimulations were delivered to the neural foramina at 100% of the stimulator capacity. The unpotentiated twitches used in the assessment of supramaximality were separated by ~30 s to avoid twitch potentiation. Potentiated twitches were used in the assessment of fatigue and were favoured over unpotentiated, as the former is considered a more sensitive measure of muscle fatigue, particularly when the degree of fatigue is

likely to be modest (Kufel *et al.*, 2002). For the inspiratory muscles, the resting $P_{di,tw}$ and peak to peak amplitude of the diaphragm electromyographic M-wave (M-$wave_{di}$) was assessed following a 1-Hz stimulation delivered to the cervical nerves immediately after a maximal inspiratory mouth pressure (MIP) manoeuvre. For the expiratory muscles, the resting $P_{ga,tw}$ and peak to peak amplitude of the abdominal electromyographic M-wave (M-$wave_{ra}$) was assessed following a 1-Hz stimulation delivered to the thoracic nerves immediately after a maximal expiratory mouth pressure (MEP) manoeuvre (Taylor *et al.*, 2006). The MIP and MEP manoeuvres were performed from RV and TLC, respectively, and maintained for ~5 s against an occluded airway. The degree of potentiation was smaller after the first and second maximal voluntary efforts; therefore, the maximal inspiratory and expiratory efforts were performed five times and the first two twitches discarded. The order of inspiratory and expiratory muscle stimulation was randomised and counterbalanced but consistent within a given participant.

6-2.12 Perceptual Responses

Ratings of the intensity of breathing discomfort (dyspnoea) were noted every 2 min during constant-power exercise and ratings of the intensity of limb discomfort were assessed retrospectively at exercise cessation, both using the modified Borg CR10 scale (Borg *et al.*, 1998). Participants were asked to rate "the intensity of breathing/limb discomfort". The end points were anchored such that zero represented "no breathing/limb discomfort" and 10 was "the most severe breathing/limb discomfort they had ever experienced or could imagine experiencing".

6-2.13 Data Capture

Cardiorespiratory responses, intra-thoracic pressures and respiratory muscle EMG were averaged on alternate 30 s intervals throughout constant-power exercise when IC manoeuvres were not being performed. Volume, flow, intra-thoracic pressures, and diaphragm EMG signals were fed through a signal amplifier (1902, Cambridge Electronic Design, Cambridge, England) and digitised at sampling rates of 150 Hz (EMG, 4000 Hz) using an analogue-to-digital converter (micro 1401 mkII, Cambridge Electronic Design, Cambridge, England). The data were displayed as waveforms using integrated data acquisition software (Spike 2 version 7.00, Cambridge Electronic Design, Cambridge, England). The abdominal EMG signals were collected using a standalone system (Trigno Lab, Delsys Inc) and retrospectively imported into the integrated data acquisition software. All EMG data were band-pass filtered (see *Electromyography*).

6-2.14 Statistics

Statistical analyses were performed with SPSS 16.0 for Windows (SPSS Inc., IBM, Chicago, IL, U.S.A). Supramaximality and pre- to post-exercise neuromuscular function was assessed via one-way, repeated measures ANOVA. In cases of statistical significance, post-hoc analyses were conducted using Bonferroni-adjusted pairwise comparisons and least-significant difference. Operating lung volumes were assessed using a two-factor (work rate * time) repeated measures ANOVA. Differences in peak physiological responses between heavy and severe work rates, in addition to within-trial twitch reproducibility data were assessed using paired-sample t-test for means. Reproducibility was assessed using the coefficient of variation and intra-class correlation. Alpha level was set at 0.05 and data expressed as mean ± S.D.

6-3 Results

6-3.1 Participants

All participants exhibited healthy pulmonary function with values for spirometry and airway resistance above the age-predicted mean (Table 6-1). Maximal inspiratory mouth pressure was +16% and MEP was -16% of the age-predicted value. $\dot{V}O_{2peak}$ during arm-cranking was 2.39 ± 0.45 $L \cdot min^{-1}$ (31.9 ± 5.3 $ml \cdot kg \cdot min^{-1}$) achieved during the severe constant-power trial. Peak power from the maximal ramp incremental exercise test was 126 ± 22 W. One participant withdrew from the study following the severe intensity constant-power trial due to discomfort using the oesophageal catheter. All data (exercise responses, neuromuscular function and supramaximality) are, therefore, presented as n=7. Three participants were asked to stop exercising at 30 min into the heavy exercise trial.

Table 6-1: Baseline Pulmonary Function

	Absolute			%Predicted		
FVC (L)	5.87	±	0.64	114	±	13
FEV_1 (L)	5.04	±	0.59	115	±	12
FEV_1 (%FVC)	85	±	2.9	94	±	4
TLC (L)	7.61	±	0.73	108	±	9
RV (L)	1.85	±	0.40	110	±	23
FRC (L)	3.53	±	0.58	107	±	17
IC (L)	4.08	±	0.45	107	±	13
PEF ($L \cdot s^{-1}$)	10.4	±	1.9	109	±	21
MVV ($L \cdot min^{-1}$)	187	±	13	108	±	8
MIP (cmH_2O)	136	±	37	116	±	36
MEP (cmH_2O)	133	±	22	84	±	15
sRaw$_{,eff}$ ($kPa \cdot s \cdot L^{-1}$)	0.68	±	0.13	58	±	11
Raw$_{,eff}$ (kPa^{-1})	0.169	±	0.033	57	±	11
DL,CO ($mmol \cdot min^{-1} \cdot kPa^{-1}$)	13.4	±	1.6	112	±	14
VA (L)	7.19	±	0.64	104	±	10
VI (L)	5.72	±	0.55	106	±	12

Mean ± S.D. n=7. Predicted values for spirometry & plethysmography from Quanjer *et al.* (1993), MVV from Neder *et al.* (1999), maximal static pressures from Wilson, Cooke, Edwards & Spiro, (1984). FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; IC, inspiratory capacity; PEF, peak expiratory flow; MVV, maximum voluntary ventilation; sRaw$_{,eff}$, specific effective airway resistance; Raw$_{,eff}$, effective airway resistance; DL,CO, diffusion capacity for carbon monoxide; VA, alveolar volume; VI, inspiratory volume.

6-3.2 Peak Cardiorespiratory and Perceptual Responses during Constant-Power Exercise

Final minute cardiorespiratory data for constant-power exercise are shown in Table 6-2 & Fig. 6-1. Exercise time for heavy and severe arm-cranking was 24.5 ± 5.8 and 9.8 ± 1.8 min, respectively. Constant-power arm-cranking at severe work rates induced slightly higher $\dot{V}O_2$ than the maximal ramp exercise test (108 ± 5%), whereas arm-cranking at heavy work rates induced $\dot{V}O_2$ values that were 80 ± 5% of the ramp protocol. Severe exercise resulted in significantly higher $\dot{V}O_2$ (p = 0.000), $\dot{V}_E$ (p = 0.02), V_T (p = 0.04), [BLa] (p = 0.01), f_C (p = 0.005), and V_T/T_I (p = 0.001). Perceptual ratings for the intensity of breathing discomfort were greater with severe exercise (p = 0.04) as were those for limb discomfort (p = 0.03). There were no work rate differences in $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, P_ECO_2, f_R, T_I, T_E, or SpO_2.

Table 6-2: Cardiorespiratory responses during the final minute of arm-cranking

	HEAVY	SEVERE
Power (W)	69 ± 18	89 ± 20*
T_{LIM} (min)	24.5 ± 5.8	9.8 ± 1.8*
$\dot{V}O_2$ ($L \cdot min^{-1}$)	1.79 ± 0.36	2.39 ± 0.45*
$\dot{V}O_2/\dot{V}O_{2peak}$ (%)	80 ± 5	108 ± 5*
$\dot{V}CO_2$ ($L \cdot min^{-1}$)	1.81 ± 0.42	2.58 ± 0.40*
RER	1.01 ± 0.06	1.09 ± 0.08**
$\dot{V}_E/\dot{V}O_2$	42 ± 15	43 ± 13
$\dot{V}_E/\dot{V}CO_2$	42 ± 14	39 ± 10
P_ECO_2 (mmHg)	23.4 ± 7.3	23.4 ± 5.6
f_C ($b \cdot min^{-1}$)	143 ± 11	163 ± 5*
$\dot{V}_E$ ($L.min^{-1}$)	73 ± 20	99 ± 19**
V_T (L)	1.70 ± 0.40	1.98 ± 0.24**
f_R ($br \cdot min^{-1}$)	47 ± 16	50 ± 11
T_I (s)	0.75 ± 0.27	0.57 ± 0.08
T_E (s)	0.78 ± 0.41	0.55 ± 0.07
T_{TOT} (s)	1.50 ± 0.69	1.17 ± 0.19
T_I/T_{TOT}	0.52 ± 0.06	0.51 ± 0.02
T_E/T_{TOT}	0.51 ± 0.05	0.49 ± 0.02
V_T/T_I ($L \cdot s^{-1}$)	2.37 ± 0.47	3.51 ± 0.03*
SpO_2 (%)	100 ± 1	99 ± 1
[BLa] ($mmol \cdot L^{-1}$)	6.4 ± 1.7	9.3 ± 2.1*
$CR10_{Dyspnoea}$	7.0 ± 2.0	8.1 ± 2.2**
$CR10_{Limbs}$	8.4 ± 1.9	10.1 ± 0.7**

Mean ± S.D. n=7. T_{LIM}, time to the limit of tolerance; $\dot{V}O_2$, O_2 uptake; $\dot{V}CO_2$, CO_2 output; RER, respiratory exchange ratio; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for O_2, $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for CO_2; P_ECO_2, partial pressure of mixed expired CO_2; f_C, cardiac frequency; $\dot{V}_E$, minute ventilation; V_T, tidal volume; f_R, respiratory frequency; T_I, inspiratory time; T_E, expiratory time; T_{TOT}, total respiratory time; T_I/T_{TOT}, inspiratory duty cycle; T_E/T_{TOT}, expiratory duty cycle; V_T/T_I, mean inspiratory flow; SpO_2, arterial oxygen saturation; [BLa], blood lactate concentration; $CR10_{Dyspnoea}$, intensity of breathing discomfort; $CR10_{Limbs}$, intensity of limb discomfort. Significantly different vs. heavy exercise *$p < 0.01$, **$p < 0.05$.

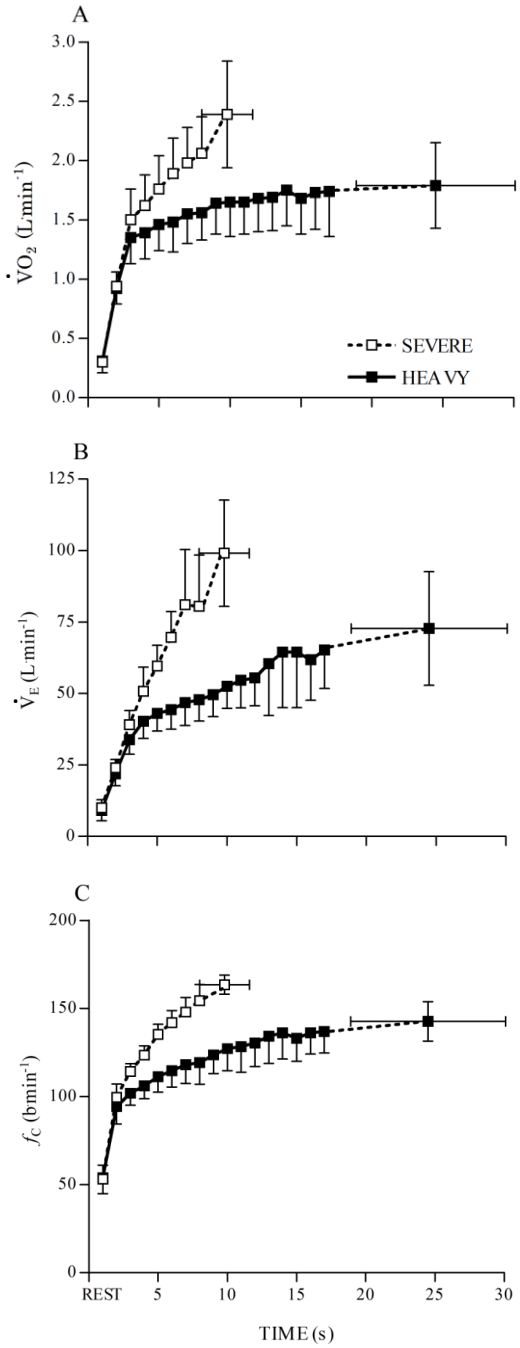

Fig. 6-1: Oxygen uptake (panel A), ventilation (panel B) and cardiac frequency (panel C) during constant-power arm-cranking at heavy and severe work rates. During severe exercise, cardiorespiratory variables increase exponentially to volitional fatigue (9.8 ± 1.8 min), but during heavy exercise cardiorespiratory indices drift upwards and almost reach steady state (24.5 ± 5.8 min). Mean ± S.D. n=7.

6-3.3 Peak Respiratory Mechanics during Constant-Power Exercise

Data on respiratory mechanics collected in the final minute of constant-power exercise are shown in Table 6-3. Respiratory pressure swings during inspiration were not different between heavy and severe work rates at rest or within 1 min of constant-power exercise (Fig. 6-2). However, the final minute of severe exercise induced significantly greater $\Delta Poe_{,insp}$ (p = 0.001), $\Delta Pga_{,insp}$ (p = 0.008), $\Delta Pdi_{,insp}$ (p = 0.002), W_b (p = 0.027), in addition to Poe/P_{IMAX} (p = 0.003) and Pga/P_{EMAX} (p = 0.005). Due to a poor digital trace in one participant, EMG_{di} and EMG_{ab} are presented as n=6. EMG_{ra} was significantly greater during severe exercise (p = 0.003) and although EMG_{di} was also greater during severe exercise, this did not reach statistical significance (p = 0.195). Operating lung volumes at rest, in the first minute and final minute of heavy and severe exercise are shown in Fig. 6-3 and Table 6-3. There were significant increases in EELV (p = 0.034) and EILV (p = 0.009) during severe exercise relative to heavy exercise showing main effects for work rate. Specifically, there were no differences in resting EELV (54 vs. 55%) or EILV (66 vs. 65%), however, within the first minute of severe exercise, EELV and EILV had increased (EELV, 52 vs. 46%; EILV, 76 vs. 66%). At the cessation of severe intensity exercise, operating lung volumes had increased above baseline (Fig. 6-3, Table 6-3).

Table 6-3: Respiratory mechanics during the final minute of arm-cranking

	HEAVY	SEVERE
EILV (%TLC)	77 ± 6	83 ± 7*
EELV (%TLC)	54 ± 7	58 ± 3**
$\Delta Pdi_{,insp}$ (cmH_2O)	33 ± 11	53 ± 13*
$\Delta Pga_{,insp}$ (cmH_2O)	13.9 ± 5.5	23.2 ± 6.8*
$\Delta Poe_{,insp}$ (cmH_2O)	19.3 ± 6.7	29.7 ± 9.3*
$\Delta Pga/P_{Emax}$ (%)	8 ± 2	14 ± 2*
$\Delta Poe/P_{Imax}$ (%)	13 ± 5	20 ± 7*
W_b ($J \cdot min^{-1}$)	168 ± 131	321 ± 169**
$EMG_{di,IN}$ (%RMS_{MAX})	50 ± 33	70 ± 23
$EMG_{ra,EX}$ (%RMS_{MAX})	31 ± 22	60 ± 10*

Mean ± S.D. n=7 (EMG, n=6). EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; $\Delta Pdi_{,insp}$, transdiaphragmatic pressure swing during inspiration; $\Delta Pga_{,insp}$, gastric pressure swing during inspiration; $\Delta Poe_{,insp}$, oesophageal pressure swing during inspiration; $\Delta Pga/P_{EMAX}$, gastric pressure swing as a % of maximal expiratory gastric pressure; $\Delta Poe/P_{IMAX}$, oesophageal pressure swing as a % of maximal inspiratory oesophageal pressure; W_b, work of breathing; $EMG_{di,IN}$, electromyographic activity of the diaphragm during inspiration; $EMG_{ra,EX}$, electromyographic activity of the rectus abdominis during expiration. Significantly different vs. heavy exercise *$p < 0.01$, **$p < 0.05$.

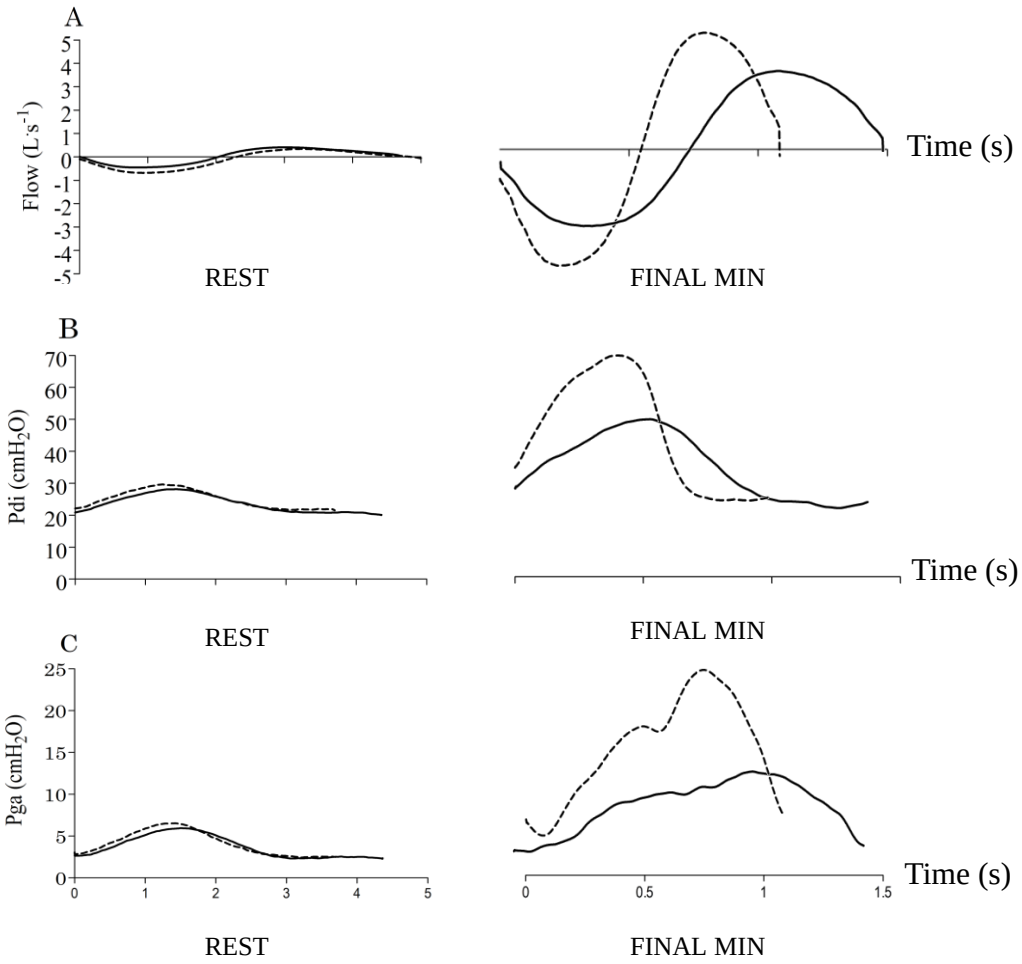

Fig. 6-2: Group mean ensemble average airflow (panel A), transdiaphragmatic pressure (panel B) and gastric pressure (panel C) at rest and during the final minute of constant-power arm-cranking performed at heavy and severe work rates. Inspiration is represented by negative airflow whereas expiration is represented by positive airflow. Respiratory airflow and intra-thoracic pressures were similar at rest but substantially greater in the final minute of severe exercise. n=7.
- - - Severe, ––– Heavy

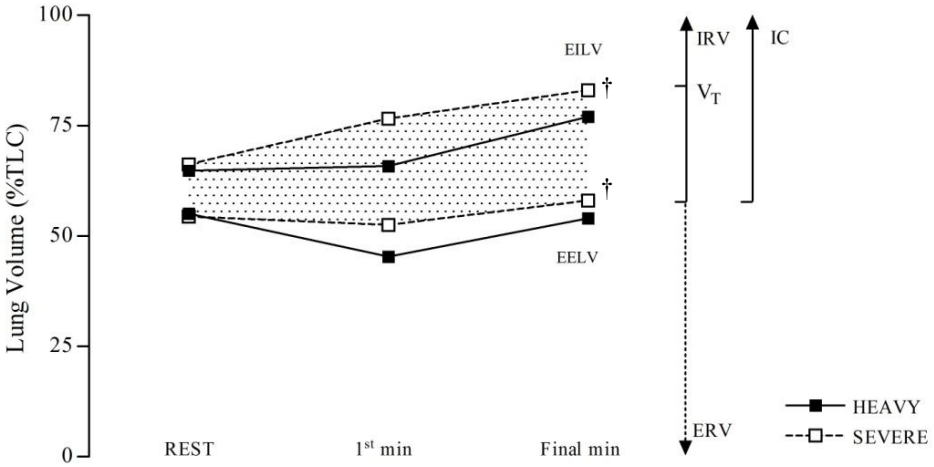

Fig. 6-3: Operating lung volumes at rest, in the first minute and final minute of constant-power arm-cranking performed at heavy and severe work rates. EELV and EILV are not different at rest but are elevated in the first minute of severe exercise. At end exercise, operating lung volumes during severe exercise increased above baseline. † Main effect for work rate; EELV ($p < 0.05$), EILV ($p < 0.01$).

6-3.4 Supramaximal Stimulation

To determine whether nerve stimulation of the diaphragm and abdominals was supramaximal, three single twitches were delivered to the relevant motor nerves at 50, 60, 70, 80, 85, 90, 95 and 100% of the stimulator output. The mean $P_{di,tw}$ and $P_{ga,tw}$ was calculated at each power. Group mean values for $P_{di,tw}$ and $P_{ga,tw}$ at each stage of the incremental protocol are shown in Fig. 6-4. $P_{ga,tw}$ appeared to level-off at 95% of stimulator output whereas $P_{di,tw}$ appeared to increase slightly. A repeated measures ANOVA with Bonferroni-adjusted pairwise comparisons indicate that there were no significant increases in $P_{ga,tw}$ (p = 1.000) or $P_{di,tw}$ (p = 0.487) when the stimulator intensity was increased from 95 to 100% suggesting that both the expiratory and inspiratory muscles were supramaximally stimulated at 100% stimulator capacity.

6-3.5 Reproducibility

To determine the within-day, between-trial reproducibility of the nerve stimulation techniques, diaphragm and abdominal muscle contractile function were assessed before and after 30 min of quiet breathing. There were no systematic differences in any of the motor evoked measurements of contractile function. Coefficient of variation for $P_{di,tw}$ and $P_{ga,tw}$ was 5.4% and 7.3%, respectively. Furthermore, all reproducibility coefficients were <9.5% (CV) and >0.6 (ICC) (Table 6-4).

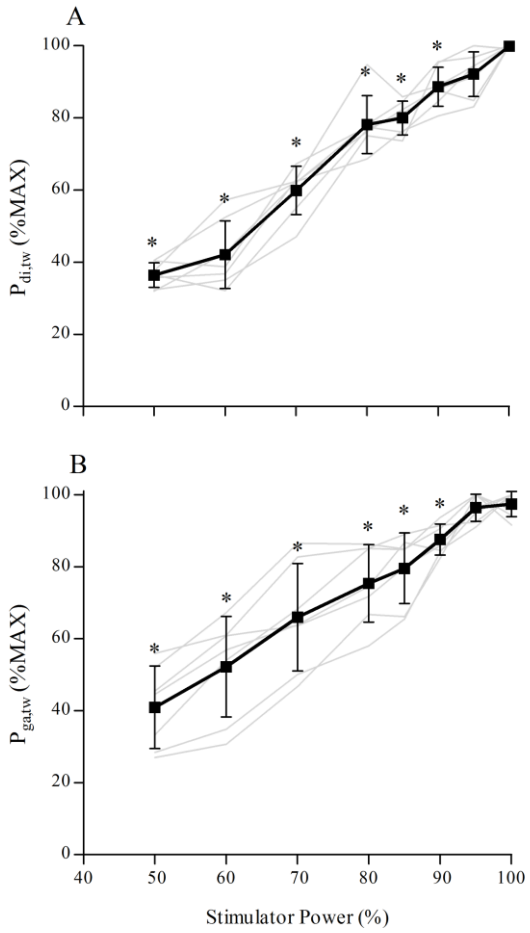

Fig. 6-4: Transdiaphragmatic twitch pressure (panel A) and gastric twitch pressure (panel B) response to incremental electromagnetic stimulation at 1 Hz. There were no significant differences in $P_{di,tw}$ or $P_{ga,tw}$ between 95 and 100% stimulator output. Individual and mean ± S.D. n=7. *Significantly different ($p < 0.05$) from 100% stimulator power. Thin lines represent individual data.

Table 6-4: Reproducibility of within-day measurements of contractile function

	Trial 1	Trial 2	CV, %	ICC (LL – UL)
Diaphragm				
$P_{di,tw}$	56 ± 14	54 ± 11	5.4	0.96 (0.78 - 0.99)
$P_{oe,tw}$	34.5 ± 6.9	35.5 ± 7.4	3.3	0.98 (0.89 - 1.00)
$P_{oe,tw}/P_{di,tw}$	0.63 ± 0.13	0.67 ± 0.14	4.8	0.96 (0.71 - 0.99)
CT (ms)	78.5 ± 6.3	83.8 ± 7.6	5.5	0.60 (-0.45 - 0.92)
$RT_{0.5}$ (ms)	63.4 ± 11.2	66.8 ± 12.3	7.5	0.81 (0.27 - 0.97)
$P_{IMAX,m}$ (cmH_2O)	128 ± 37	124 ± 38	2.9	0.99 (0.95 - 1.00)
$P_{IMAX,oe}$ (cmH_2O)	143 ± 38	138 ± 36	3.6	0.99 (0.92 - 1.00)
$P_{IMAX,di}$ (cmH_2O)	191 ± 48	185 ± 48	3.7	0.99 (0.91 - 1.00)
Abdominals				
$P_{ga,tw}$	59 ± 17	56 ± 14	7.3	0.94 (0.68 - 0.99)
CT (ms)	103 ± 30	89 ± 23	9.8	0.90 (0.10 - 0.98)
$RT_{0.5}$ (ms)	129 ± 33	127 ± 30	6.3	0.95 (0.70 - 0.99)
$P_{EMAX,m}$ (cmH_2O)	116 ± 23	117 ± 16	4.7	0.92 (0.54 - 0.99)
$P_{EMAX,ga}$ (cmH_2O)	169 ± 41	163 ± 41	3.2	0.99 (0.82 - 1.00)

Mean ± S.D. n=7. $P_{di,tw}$, transdiaphragmatic twitch pressure; $P_{oe,tw}$, oesophageal twitch pressure; CT, contraction time; $RT_{0.5}$, one half relaxation time; $P_{IMAX,m}$, maximal inspiratory mouth pressure; $P_{IMAX,oe}$, maximal inspiratory oesophageal pressure; $P_{IMAX,di}$, maximal inspiratory transdiaphragmatic pressure; $P_{ga,tw}$, gastric twitch pressure; $P_{EMAX,m}$, maximal expiratory mouth pressure; $P_{EMAX,ga}$, maximal expiratory gastric pressure.

6-3.6 Neuromuscular Function

Group mean neuromuscular function data before and after heavy and severe constant-power exercise are shown in Table 6-5. At 1 Hz stimulation frequency, 6 of 7 participants exhibited a >10% reduction in $P_{ga,tw}$ following severe arm-crank exercise. Group mean $P_{ga,tw}$ at 5 - 15 min following severe exercise fell by 22 ± 18% (p = 0.038). At 25 - 35 min post-exercise $P_{ga,tw}$ had recovered slightly (p = 0.066) but remained 15 ± 15% below baseline (Fig. 6-6). $P_{ga,tw}$ was not different following heavy exercise. Furthermore, there were no changes in $P_{di,tw}$ or $P_{oe,tw}/P_{di,tw}$ following severe or heavy exercise.

Table 6-5: Neuromuscular function measurements before and up to 35 min after exercise

	HEAVY			SEVERE		
	Pre-Ex	5 – 15 min	25 – 35 min	Pre-Ex	5 – 15 min	25 – 35 min
Diaphragm						
$P_{di,tw}$	53 ± 13	58 ± 11	57 ± 14	55 ± 10	52 ± 15	54 ± 14
CT (ms)	84.2 ± 9.7	82.4 ± 6.8	83.9 ± 13.7	86.5 ± 6.4	86.5 ± 7.6	79.8 ± 16.6
$RT_{0.5}$ (ms)	66 ± 13	60 ± 14	64 ± 10	65 ± 11	55 ± 12	60 ± 6
$P_{oe,tw}/P_{di,tw}$	0.67 ± 0.11	0.65 ± 0.11	0.66 ± 0.07	0.66 ± 0.12	0.68 ± 0.14	0.67 ± 0.10
M-$Wave_{,di}$ (mV)	3.16 ± 0.13	3.01 ± 0.22	3.00 ± 0.23	2.91 ± 0.26	2.91 ± 0.36	2.87 ± 0.43
M-$Wave_{,di}$ (ms)	1.53 ± 0.06	1.52 ± 0.23	1.45 ± 0.18	1.58 ± 0.09	1.51 ± 0.17	1.56 ± 0.07
$P_{IMAX,m}$ (cmH_2O)	119 ± 27	121 ± 39	109 ± 20	127 ± 38	126 ± 41	130 ± 39
Abdominals						
$P_{ga,tw}$	54 ± 15	54 ± 18	54 ± 18	53 ± 15	41 ± 13	46 ± 14
CT (ms)	92 ± 33	81 ± 26	81 ± 21	91 ± 24	83 ± 29	80 ± 19
$RT_{0.5}$ (ms)	133 ± 28	115 ± 29	120 ± 37	126 ± 30	120 ± 42	122 ± 30
M-$wave_{,ra}$ (mV)	2.2 ± 1.0	2.1 ± 1.0	1.7 ± 0.8	2.4 ± 1.5	2.2 ± 1.3	2.1 ± 1.1
M-$wave_{,ra}$ (ms)	13.7 ± 4.8	12.3 ± 4.6	11 ± 4	14.1 ± 3.9	14.1 ± 4.9	14.5 ± 4.3
$P_{EMAX,m}$ (cmH_2O)	118 ± 16	108 ± 22	109 ± 20	117 ± 21	119 ± 27	113 ± 24

Mean ± S.D. n=7. $P_{di,tw}$, transdiaphragmatic twitch pressure; CT, contraction time; $RT_{0.5}$, one half relaxation time; M-$Wave_{,di}$, M-wave from the diaphragm; $P_{IMAX,m}$, maximal inspiratory mouth pressure; $P_{ga,tw}$, gastric twitch pressure; M-$wave_{,ra}$, M-wave rectus abdominis; $P_{EMAX,m}$, maximal expiratory mouth pressure.

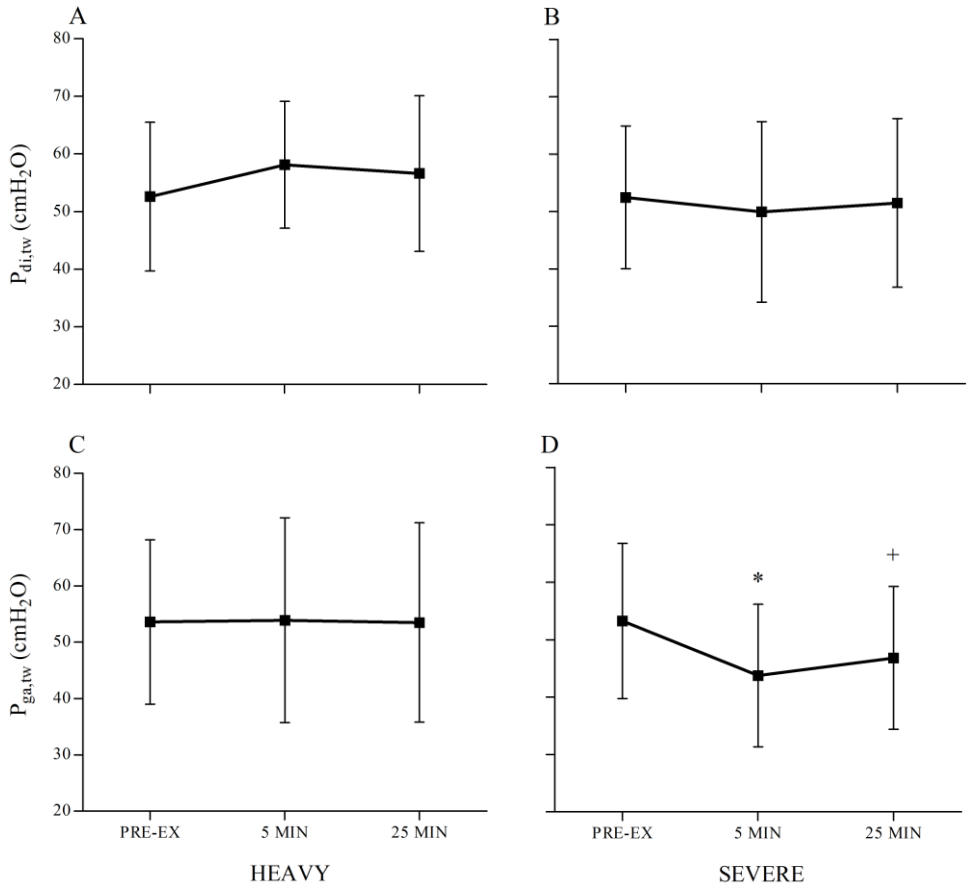

Fig. 6-5: Transdiaphragmatic twitch pressure (panels A and B) and gastric twitch pressure (panels C and D) response to electromagnetic stimulation before, 5 - 15 min and 25 - 35 min after constant-power arm-cranking performed at heavy and severe work rates. There was significant contractile fatigue of the abdominal muscles following severe exercise, with a reduction in $P_{ga,tw}$ of ~22 ± 18% at 5 – 15 min. Values had partially recovered at 25 – 35 min. Respiratory muscle fatigue did not occur in response to heavy exercise. Mean ± S.D. n=7. Significantly different ($p < 0.05$) *vs. PRE-EX, +vs. 5 – 15 min.

6-4 Discussion

This study investigated whether arm-cranking exercise performed at heavy (80 ± 5% $\dot{V}O_{2peak}$) and severe (108 ± 5% $\dot{V}O_{2peak}$) work rates to the limit of tolerance, would be of sufficient mechanical-ventilatory stress to induce contractile fatigue of the respiratory muscles in a group of healthy, able-bodied men. The main finding of this study is that severe intensity arm-cranking induced a statistically significant 22 ± 18% reduction in $P_{ga,tw}$ (6 of 7 participants >10% reduction) following magnetic stimulation of the thoracic spinal nerve-roots. By contrast, stimulation of the cervical spinal nerves following severe exercise did not induce any associated decrease in $P_{di,tw}$. Furthermore, heavy exercise did not induce contractile fatigue of the diaphragm or abdominal muscles. This study, therefore, is the first to present objective evidence that expiratory muscle fatigue occurs in healthy, able-bodied men following upper-body exercise. Importantly, severe UBE was insufficient to induce a maximal stress on the cardiorespiratory system and a further explanation for respiratory muscle contractile fatigue in this mode of exercise is required.

6-4.1 Technical Considerations

The authors favoured magnetic versus electrical stimulation for the assessment of respiratory muscle contractile function. Although electrical stimulation has been used previously to activate superficial muscles of the abdominal wall (Mier *et al.*, 1985; Suzuki *et al.*, 1999), it is ineffective at stimulating the deeper abdominal muscles that are recruited as ventilation increases (Van Gansbeke and Gorini, 1990; Abe and Kusuhara 1996). Furthermore, magnetic stimulation does not activate cutaneous pain receptors and, in accordance with previous studies (Taylor *et al.*, 2009; Polkey *et al.*, 1999), was well tolerated by the study participants.

Rather than stimulating the phrenic nerves anterolaterally as in early research (Johnson *et al.*, 1993), the inspiratory muscles were instead stimulated from the cervical and thoracic spinal foramina using a single, circular 90 mm coil (Similowki *et al.*, 1989; 1998; Taylor *et al.*, 2009). Magnetic stimulation provides a diffuse spread of current to activate a high density of nerve roots. By delivering stimulations at the cervical spine, it was possible to co-stimulate several inspiratory muscles including the diaphragm and ribcage musculature (Similowski *et al.*, 1989), thus making it possible to quantify the contribution of the latter to transdiaphragmatic pressure generation. Bilateral anterior phrenic nerve stimulation, however, isolates the diaphragm and has been shown to elicit larger $P_{di,tw}$ declines following voluntary hyperpnoea when compared to cervical stimulation (Mador *et al.*, 2002). There is the possibility, therefore, that the technique used in this study to activate the phrenic nerves led to an underestimation of diaphragm fatigue.

Stimulation of the cervical and thoracic nerve roots was supramaximal, i.e. there were no significant increases in $P_{di,tw}$ or $P_{ga,tw}$ when increasing the stimulator power from 95 – 100%. Although $P_{ga,tw}$ appeared to level-off at 95%, however, activation of the cervical nerve roots appeared to induce a slight (non-significant) increase in $P_{di,tw}$ from 95 – 100% stimulator capacity. The absence of a plateau in $P_{di,tw}$ during the incremental supramaximality trial may be due to the co-stimulation of nerves additional to the phrenics. Indeed, cervical activation may have activated nerves that innervate the ribcage muscles, external and parasternal intercostals, scalenes and deltoids. As such, these techniques may have induced supramaximal stimulation of the diaphragm, without fully activating all additional muscles of inspiration.

Every effort was made to ensure consistency within and between stimulations. Although small deviations in coil position over the intervertebral spaces may not affect $P_{ga,tw}$ (Lin *et al.*, 1998), the coil position that evoked the greatest change in intra-thoracic pressure was marked on the skin and used for subsequent stimulations. In each instance, the coil was positioned horizontally to the spine and flush to the skin. Magnetic stimulations delivered pre- to post-exercise did not result in any significant changes in diaphragm or abdominal muscle M-wave amplitude, suggesting that transmission of the stimulation was consistent (Table 6-5). Furthermore, motor-evoked twitch responses measured before and after 30 min quiet breathing, show strong reproducibility coefficients for both $P_{di,tw}$ (CV, 5.4%; ICC, 0.96) and $P_{ga,tw}$ (CV, 7.3%; ICC, 0.94). The reduction in $P_{ga,tw}$ observed following severe exercise was 22 ± 18% (n=7) which had recovered slightly at 30 min post-exercise. Since the abdominals were supramaximally stimulated during measurements, and $P_{ga,tw}$ showed strong reproducibility, the changes in $P_{ga,tw}$ pre- to post-exercise were likely due to contractile fatigue.

Finally, it has been suggested that muscle membrane conductance may be compromised for ~4 min after exercise cessation (Miller *et al.*, 1987). In this study, the post-exercise stimulation protocol commenced 5 min after volitional fatigue. This additional time allowed participant ventilation to return to normal, which facilitated the delivery of nerve stimulations at lung relaxation volume. As a result, it is unlikely that the measures of intra-thoracic twitch pressure were influenced by reduced membrane conductance. By contrast, although muscle metabolic state associated with low-frequency fatigue may take ~60 min to recover, the PCr and pH status begins to regain homeostatic balance immediately on exercise cessation. Given the 5 min recovery time used presently, and the small effects being measured, it is possible that the degree of contractile abdominal and/or diaphragm muscle fatigue was underestimated. Since constant-power exercise did not induce a change in $P_{oe,tw}/P_{di,tw}$ from baseline, it is likely that the ribcage

contribution to pressure generation was also maintained. As such, contractile function of the inspiratory muscles as a group, appear to be unaffected by high-intensity arm-cranking exercise.

6-4.2 Causes of respiratory muscle fatigue

Following severe exercise, there was a significant fall in $P_{ga,tw}$ of 22 ± 18% (6 of 7 participants >10% reduction). Inspiratory muscle fatigue is most commonly attributable to an interaction of diaphragm work (pressure generation) with exercise intensity-mediated physiological effects (Johnson *et al.*,1993). However, because cardiorespiratory stress is largely dependent on the absolute volume of skeletal muscle mass active during exercise (Bergh *et al.*, 1976), UBE is likely insufficient to induce a maximal (central) cardiorespiratory stress in healthy, able-bodied individuals. Oxygen uptake achieved during arms-only exercise is reportedly 20 – 30% lower than that induced by leg exercise (Miles *et al.*, 1989, Sawka, 1986) and even maximal UBE represents only a submaximal cardiopulmonary stress when expressed against values achieved during maximal LBE (Martin *et al.*, 1991). Although maximal exercise capacities in this study were assessed during arm-cranking, with no lower-body comparison, it is likely that participants had substantial cardiorespiratory reserve at end exercise. Indeed, $\dot{V}_E$ in the final minute of severe exercise was 99 ± 19 $L \cdot min^{-1}$, equivalent to 53 ± 10% MVV. Furthermore, ratings of breathing discomfort (dyspnoea) immediately following task failure were 8.1 ± 2.2 whereas limb discomfort was rated at 10.1 ± 0.7. These data suggest that volitional fatigue at peak exercise was more closely related to local neuromuscular factors than ventilatory. Finally, when asked at exercise cessation their reason for ending the severe intensity constant-power trial, all participants cited peripheral muscular fatigue and/or discomfort as the primary cause. These findings are in general agreement with previous observations made during arm-cranking exercise (Sawka, 1986, Sawka *et al.*, 1983).

The reduction in $P_{ga,tw}$ following exhaustive arm-cranking at severe intensities is indicative of low-frequency fatigue of the abdominal muscles. Evidence from intracellular studies suggest that fatigue in this context may be due to a reduced Ca^{2+} secretion from SR in the sarcolemma and/or damaged fibre sarcomeres resulting from overextension of the muscle during concentric and eccentric contractions (Jones *et al.*, 1996). Since $P_{ga,tw}$ had partially returned to baseline at 25 - 35 min post-exercise, the fatigue observed presently is likely due to the former. Given the low absolute cardio-ventilatory stress induced by arm-cranking exercise protocol(s), combined with subjective reports that implicate local neuromuscular factors as the principal cause of exercise cessation, it is proposed that low-frequency contractile fatigue of the expiratory muscles may be due to the locomotor mechanics associated with high-intensity arm-cranking.

6-4.3 Previous Studies on Respiratory Muscle Fatigue

Following high-intensity endurance exercise, nerve stimulation techniques have been used to demonstrate fatigue of both the diaphragm (Johnson *et al.,* 1993; Mador *et al.,* 1993; Babcock *et al.,* 1995, 1996, 1998, 2002) and abdominal muscles (Taylor *et al.,* 2006; Verges *et al.,* 2006). Respiratory muscle fatigue is likely attributable to the ventilatory requirements imposed by heavy exercise, and the magnitude of fatigue and likelihood of occurrence increases with increasing exercise intensity (Johnson *et al.,* 1993). As a result, previous studies have applied whole- or lower-body exercise protocols to induce maximal cardioventilatory strain, with a predominance assessing fatigue following lower-body cycling or treadmill running. Furthermore, peak ventilation rates of 120 – 150 $L \cdot min^{-1}$ are typically reported during exercise (Johnson *et al.,* 1993; Babcock *et al.,* 1995, 1996, 1998, 2002; Taylor *et al.,* 2006; Verges *et al.,* 2006; Robinson *et al.,* 2005).

To the author's knowledge, only two studies have assessed respiratory muscle fatigue following exercise of a relatively low ventilatory demand. In the first study, paralympic athletes with cervical spinal cord injury exhibited a $\dot{V}_{Epeak}$ of ~52 $L.min^{-1}$ during exhaustive constant-power arm-cranking exercise (Taylor *et al.,* 2010). The authors report no associated change in electromagnetically-induced diaphragm contractile function following exercise. The second study assessed diaphragm fatigue in healthy, able-bodied participants performing cycle ergometry to exhaustion (Mador *et al.,* 1993*).* Their participants exhibited a $\dot{V}_{Epeak}$ of ~90 $L \cdot min^{-1}$ which induced a post-exercise reduction in $P_{di,tw}$ of ~17%. Abdominal muscle contractile function was not assessed in their study. The present study is the first, therefore, to observe a decrease in expiratory muscle strength following severe intensity upper-body exercise of a submaximal ventilatory stress. Collectively, these data suggest that arm-cranking places additional (non-respiratory) demands on the major expiratory muscles that compromise contractile function.

The magnitude of abdominal muscle fatigue in this study (22 ± 18%) is in accordance with some studies assessing the expiratory muscles (25%, Taylor *et al.,* 2006) and higher than others (11.3%, Verges *et al.,* 2006). A recent case-study from this laboratory demonstrated a reduction in electromagnetically-induced $P_{di,tw}$ of 33% in a single male Paralympic oarsman performing an arms-only rowing time trial on an adapted rower (Tiller, Aggar, West & Romer, 2014). Although the second half of the time trial induced neuro-mechanical uncoupling, which may have contributed to diaphragm fatigue, the athlete demonstrated exceptional lung function and cardiovascular capacity and reached a peak ventilation of 154 $L \cdot min^{-1}$. As such, the influence of high ventilatory drive on this instance of diaphragm fatigue cannot be discounted.

6-4.4 Diaphragm and Abdominal Muscle Function During UBE

In this study, expiratory, but not inspiratory muscle fatigue was observed following high-intensity arm-cranking. These observations may be explained by considering the relative roles of the respiratory muscles during UBE. Indeed, the diaphragm receives multiple neural inputs from the cerebral respiratory centres, non-respiratory higher centres primarily for postural drive, and several peripheral sources (Hodges and Gandevia, 2000). The diaphragm's primary role is in ventilation, and on contraction will flatten to increase the vertical dimensions of the thoracic cavity to facilitate inspiration. It is generally accepted that the diaphragm has supportive postural roles, and diaphragm EMG increases during static postural (Hodges *et al.*, 1997) but not isometric rotational (Hudson *et al.*, 2010) contractions. There is strong evidence, however, to suggest that the diaphragm can only coordinate both its postural and respiratory functions during brief, intermittent disturbances to trunk stability (such as brief arm movements). When the chemical drive to breathe results in an increase in $\dot{V}_E$, pontomedullary respiratory input to the diaphragm is prioritised and postural drive to the phrenic motoneurons is simultaneously withdrawn (Hodges *et al.*, 2001). It may be that when PCO_2 levels increase, feed-forward protective mechanisms exist to prioritise essential respiratory functions of the diaphragm in an effort to regulate pH and maintain homeostatic balance (Hodges *et al.*, 2001). Severe arm-cranking exercise in this study induced a ventilatory demand that was relatively modest, i.e. 99.1 ± 18.6 $L.min^{-1}$ (53 ± 10% MVV). Combined with the likely diminished postural input to the diaphragm, it is proposed that arm-cranking was of insufficient ventilatory demand to induce contractile fatigue of the diaphragm. Indeed, previous studies (Johnson *et al.*, 1993; Mador *et al.*, 1993; Babcock *et al.*, 1995, 1996, 1998, 2002; Taylor *et al.*, 2006; Verges *et al.*, 2006) have observed diaphragm fatigue following whole- or lower-body exercise of a greater ventilatory demand (~120 – 150 $L{\cdot}min^{-1}$).

By contrast, the abdominals may undergo excessive loading during dynamic UBE in carrying out a series of interrelated mechanical functions. While expiration at rest occurs passively as a result of ribcage and abdominal wall elastic recoil (West, 2005), exercise requires regular, forceful contractions of the major expiratory muscles to reduce EELV below relaxation volume, and thereby expand tidal volume (Dempsey *et al.*, 1996). The abdominals also contract isotonically to flex, laterally flex and rotate the vertebral column during dynamic UBE, i.e. arm-cranking (Tortora and Grabowski, 2003). Because severe exercise in this study required a significantly greater external power output compared to heavy exercise (89 ± 20 vs. 69 ± 18 W), abdominal muscle participation in locomotion was likely exacerbated. Indeed, relative to heavy exercise, severe exercise resulted in significantly elevated EMG_{ra} (31 ± 22 vs. 60 ± 10 $\%RMS_{MAX}$,) reflecting markedly elevated neural drive, in addition to greater $\Delta Pga_{,insp}$ (13.9 ± 5.5 vs. 23.2 ±

6.8) reflecting expiratory muscle force output (Table 6-3, Fig. 6-2). Greater mechanical loading on the expiratory muscles was likely a principal cause.

The crank strategy employed by participants may also contribute to expiratory muscle work during arm-cranking. Indeed, increasing the force applied to the crank shaft by using a low arm-crank cadence (50 – 60 rev·min^{-1}) at given power output, leads to an increase in trunk rotation and shoulder range of motion (Price *et al.,* 2007) in an effort to recruit greater functional muscle mass in the movement to overcome the increased flywheel inertia. Low cadences may, therefore, increase the thoracic locomotor contribution. By contrast, Chapter 5 presented indirect evidence to suggest that high cadences (70 – 90 rev·min^{-1}) may result in greater static postural demands of the thoracic muscles in order to resist the spinal disturbances caused by greater impact loading through the torso. It may be that crank strategies employing moderate crank frequencies, i.e. 60 – 70 rev·min^{-1} represent a mechanically optimal 'green zone' which balances the locomotor and postural loads of arm-cranking. Since this study imposed a crank rate of 75 rev·min^{-1} during the constant-load trials, the crank strategy likely contributed to a relatively higher isometric work component than would be expected at a low cadence.

There may be additional loads placed on the expiratory muscles in order to balance the ventilatory functions of other accessory respiratory muscles. Since static diaphragm contractions contribute to the maintenance of Pga during exercise (Hodges *et al.,* 2001), an exercise ventilation-induced reduction in diaphragmatic postural drive may cause a shortfall in intra-thoracic pressure which is important in the control of spinal stability (Creswell *et al.,* 1992; Hodges *et al.,* 2001). Since the reactive forces associated with upper-limb movement may disrupt the relationship between adjacent spinal vertebrae (Panjabi *et al.,* 1989) and the orientation of the spine (Hodges *et al.,* 1999), a withdrawal of postural input to the diaphragm may necessitate compensatory mechanisms, such as increased activity of additional trunk muscles, in order to avoid injury to the spinal column. The superficial abdomen has been shown to contract phasically during repetitive arm movements (Zedka and Prochazka, 1997) with no respiratory modulation (Hodges and Gandevia, 2000) and is likely, therefore, the principal antagonist in the maintenance of Pga. The abdomen also contracts phasically during hyperpnoea to reduce diaphragm energy consumption (Finucane & Singh, 2009) possibly to preserve the diaphragmatic contribution to ventilation. During dynamic UBE, therefore, the abdominals are likely additionally recruited to aid in the maintenance of postural integrity to accommodate the shortfall in Pga and preserve diaphragm respiratory functions. The increasing use of the expiratory muscles in compensating for the reduced diaphragm work may distort the chest wall (Goldman, Grimby & Mead, 1976; Grimby,

Goldman & Mead, 1976) and reduce the mechanical efficiency of breathing (Dodd, Yarom, Loring & Engel, 1988). The abdominals undergo substantial loading during high intensity UBE, and a large proportion of abdominal muscle recruitment during such tasks appears to be independent of expiratory function. It is the UBE-induced exacerbation of abdominal muscle contractile work that is the proposed mechanism underpinning the expiratory muscle fatigue observed in the absence of maximal cardioventilatory stress.

6-4.5 Operating Lung Volumes

Additional loading of the major expiratory muscles during arm-cranking, as discussed, may result in a relative inability to reduce EELV during forced expiratory efforts, such as those required during high-intensity exercise. At peak exercise, mean expiratory time was 0.55 ± 0.07 s with expiratory flow rates exceeding 4.5 $L.s^{-1}$. Greater airflow during severe exercise suggests that the expiratory muscles were required to produce substantial hyperpnoea under great velocity of shortening. This mechanical function can only be achieved by forceful, dynamic contractions of the major expiratory muscles, increasing intra-thoracic pressure to reduce EELV. Reducing EELV during exercise aids subsequent inspiration by optimising diaphragm length (Grimby *et al.*, 1976, Grassino *et al.*, 1981, Henke *et al.*, 1988), and improving respiratory compliance (Stubbing *et al.*, 1980), thereby promoting respiratory efficiency. The assessment of operating lung volumes in this study shows a relative dynamic hyperinflation from the first minute of severe exercise which was sustained and exacerbated through to exhaustion, i.e. EELV ($p < 0.05$) and EILV ($p < 0.01$) were significantly greater in the final minute of severe versus heavy exercise. There was, therefore, an inability of the expiratory muscles to effectively reduce EELV during high-intensity arm-cranking despite an expansion of V_T. Work of breathing was greater at severe work rates (168 ± 131 vs. 321 ± 169 $Joules \cdot min^{-1}$). Although this could be the result of greater ventilatory demands at severe work rates, increased EELV has also been shown to exacerbate the work of breathing (Ferguson, 2006) since the inspiratory muscles must overcome additional elastic loads presented by the lung and chest wall (Milici-Emili and Petit, 1960; Alison *et al.*, 1998).

Dynamic hyperinflation is commonly observed in individuals with obstructive lung disease in order to avoid expiratory flow limitation (Hannink *et al.*, 2010; Alison *et al.*, 1998; Grimby and Stiksa, 1970; Potter *et al.*, 1971; Dodd *et al.*, 1984; O'Donnell and Webb, 1993) and relates to the specific pathology of the disease. Although not measured in the present study, it is unlikely that the increase in EELV was due to EFL. First, the participants all demonstrated healthy pulmonary function (Table 6-1) and were free from obstructive respiratory disorders. Second, data from Chapter 4, in addition to published research (Alison *et al.*, 1998) suggest that recreationally-active

adults do not experience expiratory flow limitation during arm-cranking exercise due to the low ventilatory demands.

In the absence of EFL, a more likely explanation for the relative dynamic hyperinflation observed is the specific motor mechanics of UBE which compromises the expiratory functions of the rectus abdominis. The diaphragm and parasternal intercostals have a pronounced postural drive that share common neural pathways with efferents for inspiratory drive, i.e. they both depolarise the same phrenic motoneurons (Hodges *et al.,* 2001; Hudson *et al.,* 2010). As a result, when physical activity increases the requirements for pulmonary ventilation, pontomedullary input has a 'gating' effect on the neural inputs controlling posture. By contrast, the abdomen plays an essential role in reducing EELV during forced expiration (Dempsey *et al,* 1996) while simultaneously working to flex and rotate the trunk (Tortora & Grabowski, 2003), functions which do not appear to be modulated during periods of exacerbated postural demand (Hodges *et al.,* 2001). Multi-tasking in this way may reduce the mechanical efficiency of the abdominals in performing both tasks simultaneously, compared to performing tasks in relative isolation. During dynamic UBE, the result is the inability to reduce EELV (Alison *et al.,* 1998).

Finally, it is unlikely that low-frequency abdominal muscle fatigue itself contributed to the increase in EELV so early in the constant-power trial (within 1 min). Expiratory muscle fatigue is not considered to play a regulatory role in operating lung volumes during high-intensity exercise (Taylor *et al.,* 2013), although this has not been assessed in the context of arm-cranking which likely imposes a mechanical restriction on the ribcage (Takano *et al.,* 1993). More importantly, however, the time duration was insufficient to substantially attenuate SR-mediated Ca^{2+} secretion or disrupt muscle metabolic state; the two principal causes of low-frequency fatigue (Miller *et al.,* 1987). Instead, there may a causal mechanism by which dynamic increases in EELV may contribute to expiratory muscle contractile fatigue by increasing the elastic work of breathing (Ferguson, 2006).

6-4.6 Implication of Findings

Respiratory muscle fatigue may impact on exercise tolerance via a number of interrelated mechanisms. Relative alveolar hypoventilation would be expected to occur following respiratory muscle fatigue, particularly if the respiratory muscles were unable to generate sufficient intra-thoracic pressures (Romer & Polkey, 2008). Compromised ventilatory responses may result in an increased intensity of dyspnoea (Gandevia, Killian & Campbell, 1981; Suzuki, Suzuki, Ishii, Akahori & Okubo, 1992). Given the relatively greater neural respiratory drive associated with

arm-cranking, as observed in Chapter 4, a reduction in mechanical-ventilatory capacity due to contractile fatigue, may further disrupt the causal relationship between neural drive and ventilatory output.

A likely mechanism by which fatigue in the present context may reduce exercise performance is via a fatigue-induced metaboreflex response, which increases sympathetic vasoconstrictor outflow and reduces vascular perfusion of the upper-limbs involved in locomotor activities (Dempsey, Romer, Rodman, Miller & Smith, 2006). This may, in turn, limit the ability of the muscle to perform work. Harms *et al.* (1997) applied graded resistive loads to the inspiratory muscles to increase total work performed, and observed a reduction in limb vascular conductance and reduced blood flow. As previously discussed, the abdominal muscles were progressively loaded during UBE by forced expiration, locomotor activity, reactive postural control, and via additional static contractions by way of compensation for diaphragm postural withdrawal. It may be that upper-limb vascular conductance was reduced as a result of the increased expiratory muscle demands. A reduction in blood flow to the working upper-limb muscle would be expected to limit exercise tolerance via increases in limb fatigue and dyspnoea, as observed when the inspiratory muscles are loaded prior to exercise (McConnell & Lomax, 2006). Further studies are needed to test this hypothesis during UBE, which has the added complication of the fact that certain respiratory muscles, i.e. abdominal and external intercostals, also contribute substantially to locomotion. There may be strong repercussions of contractile expiratory muscle fatigue for those with obstructive lung disease, since an inability to produce adequate neural drive to the respiratory muscles, perhaps resulting from contractile fatigue, may lead to ventilatory failure (McKenzie *et al.*, 2009) which places the patient at a high risk of death (Budweiser, Jorres & Pfeifer, 2008). This raises important questions regarding the appropriateness of UBE for use in pulmonary rehabilitation programmes in COPD (Similowski, Whitelaw & Derenne, 2002). See *General Discussion* for an elaboration of these implications.

6-4.7 Summary

Using nerve stimulation techniques, this study found objective evidence of abdominal muscle fatigue following severe- but not heavy-intensity upper-body exercise performed to the limit tolerance in a group of healthy participants. There was no concurrent fatigue of the diaphragm at either exercise intensity. The abdomen participates in forced expiration and postural control. During arm-cranking there are additional dynamic locomotor functions in flexing and rotating the trunk and shoulders, and abdominal demands may be further exacerbated via compensatory roles in maintaining intra-thoracic pressures and spinal integrity. By contrast, the diaphragm prioritises

ventilatory function during exercise and postural drive is subsequently withdrawn. It is proposed, therefore, that UBE is of insufficient ventilatory stress to induce contractile fatigue of the inspiratory muscles in healthy, able-bodied participants, but causes expiratory muscle fatigue through a combination of mechanical, postural and ventilatory demand. The abdominals may be particularly susceptible to low frequency fatigue during this mode of exercise, which may have important implications for both clinical practice and athletic performance.

Chapter Seven

GENERAL DISCUSSION

7-1 Introduction

This thesis presented three experimental chapters that collectively assessed the functions of the respiratory system during upper-body exercise. The aims outlined were: 1) to characterise cardiorespiratory responses and respiratory mechanics during UBE performed by healthy adults, 2) to assess the acute influence of cadence and work rate on respiratory mechanics to further understand the mechanisms that underpin the mechanical-ventilatory responses to UBE, and 3) to objectively assess whether UBE was sufficient to induce contractile fatigue of the respiratory muscles. This concluding chapter will briefly review the novel findings of the thesis before providing a mechanistic overview of the main findings in which a model for the healthy respiratory responses to UBE will be proposed. Based on the existing literature, a discussion is put forth concerning the potential implications of UBE for respiratory function. The chapter closes with recommendations for future research.

7-2 Main Findings

Chapter 4, *Breathing Mechanics During Upper- Versus Lower-Body Exercise in Healthy Humans*, characterised the 'typical' respiratory responses of healthy participants to UBE with a multi- work rate comparison to ventilation-matched LBE. Neural respiratory drive was assessed using an oesophageal balloon catheter and surface electromyography of the rectus abdominis, and operating lung volumes calculated using IC manoeuvres during exercise. The initial findings of chapter 4 reflect those of previous studies comparing arm-cranking and leg-cycling, i.e. UBE at given level of $\dot{V}_E$ resulted in constrained V_T with increases in f_R at higher intensities. Moreover, there were two crucial observations not previously reported in the literature. First, neural respiratory drive was greater at any given ventilation during UBE compared to LBE. Second, there was a significant increase in EELV during peak UBE, in the absence of expiratory flow limitation.

Chapter 5, *Effect of Cadence and Work Rate on Respiratory Mechanics During Arm-Cranking Exercise in Healthy Humans*, assessed the influence of cadence and exercise intensity on cardiorespiratory and mechanical-ventilatory responses to arm-cranking, with an aim to further understand the mechanisms that underpin the respiratory responses to UBE. The main findings were that moderate intensity exercise at high cadences induced greater cardiorespiratory stress, higher intra-thoracic pressure swings and a greater prevalence of locomotor-respiratory coupling than low cadences. These responses were likely the result of greater postural demands at high cadences causing antagonistic loading of the thoracic muscles. This was the first study to observe an effect of cadence on respiratory entrainment patterns during UBE.

Chapter 6, *Respiratory Muscle Fatigue in Response to Upper-Body Exercise in Healthy Humans*, assessed the potential implications of UBE on respiratory muscle contractile function across two exercise intensities. Neuromuscular function was assessed pre- and post-exercise using magnetic nerve stimulation. The study is the first to demonstrate objective evidence of expiratory muscle contractile fatigue in response to high-intensity UBE. It was proposed that while the inspiratory muscles do not exhibit a reduction in contractile function in response to UBE due to insufficient ventilatory demands, the major expiratory muscles, i.e. rectus abdominis, fatigue due to the combined effects of ventilatory, postural and locomotor stress induced by UBE.

7-3 Mechanistic Overview

Symmorphosis postulates that, in biological organisms, structural design is matched to functional demand (Weibel, Taylor & Hoppeler, 1991). In the context of respiratory function, the structural characteristics of the 'respiratory muscles' and the neural control of breathing are sufficiently *designed* and regulated to meet the ventilatory demands of exercise (Wiebel, Richard, Taylor, 1992). Although this hypothesis holds in healthy humans performing lower- or whole-body exercise, individuals with respiratory disease exhibit a quantitative mismatch between design and function, and exercise capacity is frequently limited by the respiratory system. Based on new data presented in this thesis, it is now evident that UBE also has the capacity to compromise respiratory function by increasing neural drive for a given ventilation, causing dynamic hyperinflation, and inducing substantial fatigue of the major expiratory muscles. From the data presented, in addition to that from previous literature, an integrated model of the primary mechanisms that underpin the respiratory responses to UBE is proposed (Fig. 7-1). Respiratory mechanics and the mechanisms that may compromise respiratory function during UBE will be discussed in the context of this model.

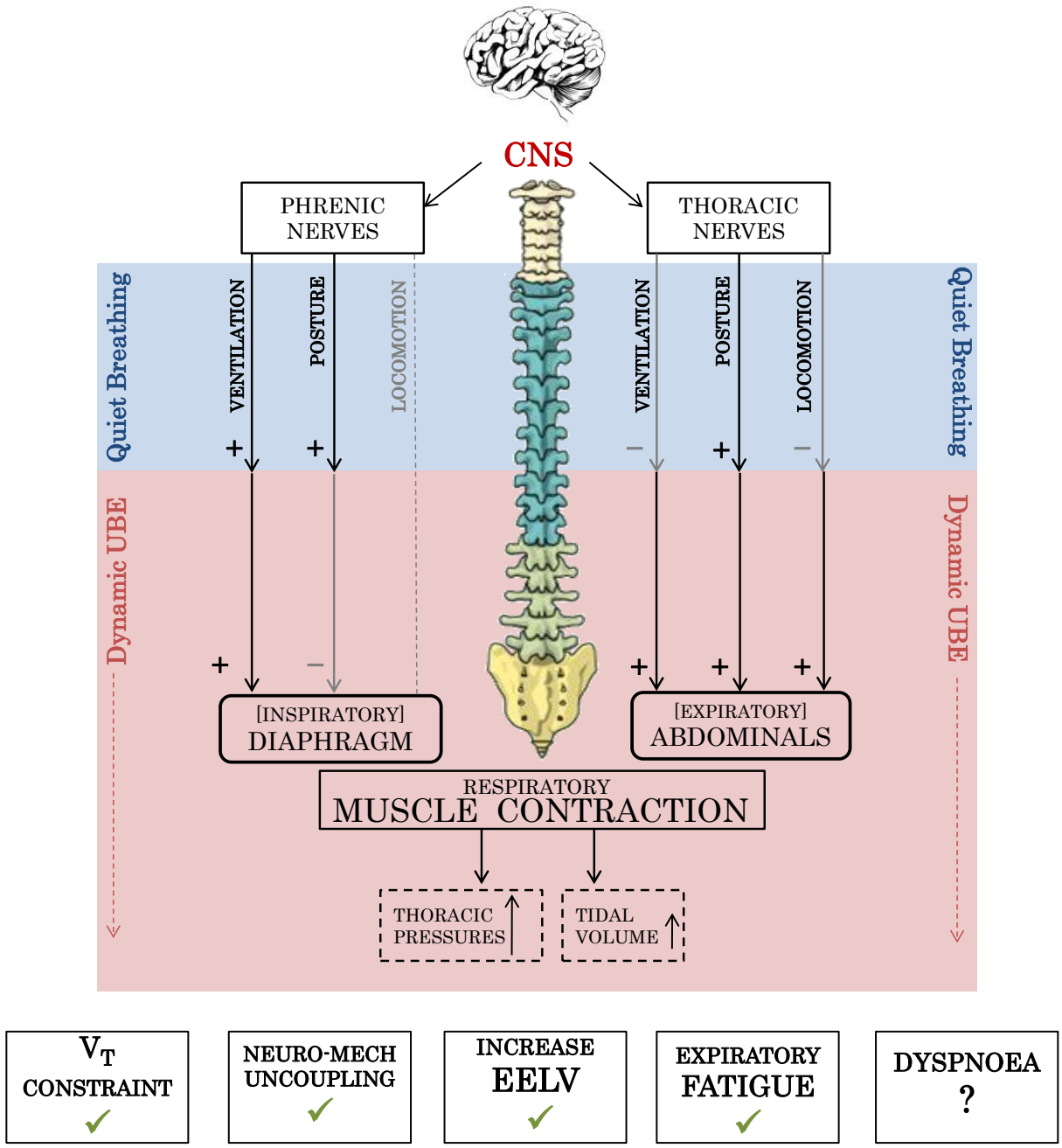

Fig. 7-1: A simplified conceptual model on the theoretical patterns of neural respiratory drive to the diaphragm and abdominal muscles, and subsequent mechanical responses to quiet breathing and dynamic upper-body exercise. During quiet breathing, the diaphragm receives pontomedullary input from the respiratory centres as well as non-respiratory input for postural support. The abdominals contract isometrically for posture but only contribute to ventilation during forced expiration, i.e. during exercise. During UBE, when the chemical drive to breathe increases, postural drive to the diaphragm is withdrawn and the abdominals receive neural drive from multiple inputs for several interrelated proactive and reactive functions. Intra-thoracic pressures increase as a result, but with a disproportionately low mechanical response (i.e. low V_T). The result is a constraint of V_T, neuro-mechanical uncoupling, dynamic increases in EELV, and expiratory muscle fatigue. The influence on dyspnoea is unclear. Original Image.

The diaphragm's ventilatory contribution is controlled by respiratory centres in the pons and medulla. On inspiration during quiet breathing, the diaphragm's parietal pleura descends into the thoracic cavity allowing the lungs to expand, and contributes approximately 75% to the increase in thoracic volume, with the remaining 25% attributable to ribcage movement controlled by the external intercostals (West, 2005; Naish, Revest & Syndercombe Court, 2009). By contrast, the major expiratory muscles (rectus abdominis, internal and external obliques, transverse abdominis) do not exert ventilatory functions during quiet breathing during which expiration is achieved via passive recoil of the ribcage and abdominal wall (West, 2005). Instead, the expiratory muscles are recruited during forced expiration when flow rate must increase during exercise. Postural drive to the diaphragm and abdominals results in isometric contractions that function to maintain intra-abdominal pressure and, therefore, stiffness of the lumbar spine (Hodges, Eriksson, Shirley & Gandevia, 2005). Non-impact LBE, i.e. cycling, does not involve the upper-limbs in locomotor activities, and requires comparatively small contributions of the thoracic muscles for postural support. This leaves the primary respiratory muscles relatively unimpeded to efficiently ventilate the lungs. During dynamic UBE, however, the respiratory muscles are tasked with maintaining adequate levels of pulmonary ventilation while simultaneously participating in additional non-respiratory tasks. The additional work, that is extraneous to the generation of pulmonary ventilation, may be loosely categorised into proactive (dynamic locomotor) or reactive (static postural) muscle contractions, both of which are exacerbated by UBE. In the context of the proposed model, the term 'proactive' may be defined as *'initiating change rather than reacting to events'*, whereas 'reactive' may be defined as *'responding or reacting to a stimulus'* (Farlex Dictionary, 2009)

Proactive Contractions

These are dynamic locomotor contractions from muscles that are principally involved in generating external power. While such contractions occur to some extent in all body movements, e.g. arm-swinging during ambulation, the forces transmitted through the upper-limbs are greatest during closed-kinetic exercises (e.g. arm-cranking) or when overcoming an external resistance (e.g. swimming). During arm-cranking, muscles of the arms, chest and shoulders dynamically contract to overcome the inertia of the flywheel and engage the ergometer propulsion system. However, even when exercising at low intensities, the rotational trunk movements required to propel the crank shaft are achieved, in part, by forceful contractions of the rectus abdominis, internal and external obliques to flex and rotate the trunk (Martini, Timmons & Tallitsch, 2012). Furthermore, since the volume of active mass during UBE is comparatively small, additional muscles of the thoracic cage are recruited to exert greater external power. Reducing ergometry

cadence rate, for example, increases the duty cycle, thereby increasing the effective forces transferred through the crank shaft at a given power output (Sanderson, 1991; Sanderson *et al.*, 2000). The result is greater shoulder and trunk range of motion in an effort to recruit greater active muscle mass into locomotion (Price *et al.*, 2007). Chapters 4 and 6 demonstrate the extent to which the rectus abdominis is additionally loaded during upper- versus lower-body locomotor activities, and the positive relationship between UBE intensity and abdominal muscle activation, respectively.

Reactive Contractions

These are static postural contractions of trunk musculature, engaged principally to counteract disturbances to spinal stability caused by limb movement (Friedli, Hallett & Simon, 1984; Hodges & Gandevia, 2000). During arm-cranking, force through the upper-limbs during locomotion is transferred to the thoracic cage, resulting in reactive postural contractions of the surrounding muscles. Reactive muscular contractions include those initiated by feed-forward mechanisms that increase EMG activity of respiratory muscles like the diaphragm, prior to activation of the upper-limb prime movers (Hodges *et al.*, 1997). In this context, static postural contractions may, therefore, be considered both reactive and pre-emptive. Since isometric contractions have been shown to elicit the same O_2 uptake per unit of muscle mass as dynamic muscle contractions (Elder *et al.*, 2006), static postural contractions of the respiratory muscles are likely sufficient to substantially increase the O_2 cost of exercise, as proposed in Chapter 5. Furthermore, because reactive muscle contractions do not directly contribute to locomotion or force development, exercises that impose large reactive forces, such as those induced by high cadence arm-cranking, are likely to negatively impact on mechanical efficiency (Price and Campbell, 1997; Smith *et al.*, 2001; Smith *et al.*, 2006a; Smith *et al.*, 2006b; Price *et al.*, 2007).

Spinal stability during exercise is maintained by the synergistic actions of both the diaphragm and abdominal muscles which create a 'hydraulic effect' in the abdominal cavity. The result is an increase in intra-abdominal pressure which aids in stiffening the lumbar spine (Hodges *et al.*, 2005). The ventilatory and postural functions of the diaphragm appear to be modulated during brief, intermittent arms movements (Hodges & Gandevia, 2000). As dynamic exercise stimulates the chemical drive to breathe, however, pontomedullary respiratory drive to the diaphragm increases and attenuates postural inputs to the phrenic motoneurons. This 'occlusion' of postural action ensures that the diaphragm's ventilatory function is prioritised (Hodges *et al.*, 2001). The response is, presumably, a protective evolutionary trait to facilitate metabolic homeostasis by prioritising O_2 delivery to body cells and elimination of H^+ and CO_2. Thus, the contribution of the

diaphragm to reactive contractions during UBE is likely to be minimal. The withdrawal of postural drive to the diaphragm, however, may cause a shortfall in gastric pressure which is important in the control of spinal stability (Creswell *et al.,* 1992; Hodges *et al.,* 2001). The external forces associated with upper-limb movement may disrupt the relationship between adjacent spinal vertebrae (Panjabi *et al.,* 1989) and the orientation of the spine (Hodges *et al.,* 1999). As such, a withdrawal of postural input to the diaphragm necessitates a series of compensatory reactive contractions from surrounding thoracic muscles in order to avoid injury to the spinal column (described above). Since the superficial abdomen contracts phasically during repetitive arm movements (Zedka and Prochazka, 1997) with no respiratory modulation (Hodges and Gandevia, 2000), it likely contributes a substantial amount of the compensatory work in maintaining Pga during UBE, thus making it particularly susceptible to fatigue. Finally, as a consequence of thoracic muscle loading, it is reasonable that participants would more frequently engage in locomotor-respiratory coupling. The phase-locking of locomotor and respiratory frequencies helps in reducing mechanical interactions between locomotion and ventilation. During UBE, adjusting the entrainment pattern to coincide with a mechanically compatible period of the locomotor cycle, may minimise antagonistic loading of the respiratory muscles and facilitate respiratory flow (Daley, Bramble and Carrier, 2013).

By requiring the upper-limbs and select thoracic muscles to perform dynamic locomotor activities, thereby increasing the external loads that are transmitted through the upper-limbs and torso, UBE results in a complex series of muscular contractions that markedly influence respiratory function. The degree to which UBE impacts on respiratory function, depends on the presence or absence of respiratory disease and spinal disorders. In healthy, able-bodied participants, respiratory mechanics will be affected by the intensity and duration of exercise, trained status and respiratory muscle strength.

7-4 Functional Implications in Health

The consequences of additional thoracic muscle loading on respiratory mechanics during UBE are pronounced. Since all primary and secondary muscles of respiration must attach to the ribs, accessory (non-respiratory) muscular contractions during UBE may produce substantial distortions and stiffening of the ribcage (Kenyon *et al.,* 1997), particularly when intra-thoracic pressures are increased. Stiffening of the ribcage and abdominal wall may inhibit the expansion of V_T during UBE, as observed in Chapter 4. Consequently, any increase in $\dot{V}_E$ during UBE is achieved predominantly via increases in f_R (Takano *et al.,* 1993; Alison *et al.,* 1998; Cerny and Ucer, 2004; Hannink *et al.,* 2010), possibly in an effort to minimise the work of breathing (Milic-

Emili, 1986). Such respiratory patterns, however, increase ventilation dead space which may lead to alveolar-ventilation perfusion mismatching and reduced exercise performance (Thin *et al.*, 2004). Although elevated ventilatory equivalents were observed during UBE in Chapter 4, the subsequent impact on exercise performance was not assessed and requires further study.

During LBE, the major expiratory muscles (rectus abdominis, external obliques) are primarily responsible for reducing EELV to expand V_T (Grimby *et al.*, 1976; McClaran *et al.*, 1995). Dynamic locomotor activity involving the upper-body, i.e. arm-cranking, increases the contractile demands on the expiratory muscles and appears to result in a relative inability to control EELV. In Chapter 5, high cadence arm-cranking did not substantially influence EELV. Although this may be due to the exercise bout being of insufficient duration to allow a steady-state $\dot{V}_E$, it may be that reactive postural loading of the respiratory muscles induced by high cadences by itself was insufficient to affect operating lung volumes. In Chapter 6, however, arm-cranking during severe exercise induced a more pronounced increase in EELV than heavy exercise. As such, the magnitude of the increase in EELV during constant-power UBE is likely to be intensity-dependent. Ventilating at elevated lung volumes results in decreased airway resistance and increased elastic recoil to aid expiration (Alison *et al.*, 1998; Porto *et al.*, 2009; Hannink *et al.*, 2010) and, as such, may be a favourable response for those with obstructive lung disease. In healthy participants, however, an increase in EELV results in shortening of the inspiratory muscles at end expiration, and is deemed mechanically disadvantageous since the inspiratory muscles must overcome the additional elastic load presented by the lung and chest wall (Milici-Emili and Petit, 1960) which increases the work of breathing. This, in turn, may contribute to the elevated dyspnoea experienced by healthy participants during UBE compared to LBE (Celli *et al.*, 1985) which may reduce exercise tolerance (ATS, 2012). An additional consequence of the dynamic increase in EELV, is that the metabolic and circulatory costs of a high work of breathing can contribute ~ 10% of the $\dot{V}O_{2max}$ in untrained participants (Aaron, Johnson, Seow & Dempsey, 1992), and ~ 16% $\dot{V}O_{2max}$ in trained participants (Harms *et al.*, 1998). As such, these UBE-induced respiratory mechanics can negatively impact exercise tolerance in patients and athletes alike. There is also a reduction in the mechanical advantage of the diaphragm when operating at higher lung volumes which may, in part, result in exercise-induced respiratory muscle fatigue (Romer and Polkey, 2008), as observed in Chapter 6.

During UBE, descending neural signals from the CNS result in contractions of the muscles that are integrated into the thoracic cage, thereby increasing intra-thoracic pressures. In chapter 4, neural drive (EMG_{ra} and Poe) was greater during UBE compared to LBE at a given $\dot{V}_E$. UBE,

therefore, has the capacity to induce increases in neural respiratory drive without subsequent increases in $\dot{V}_E$. Furthermore, since V_T was lower due to UBE-induced mechanical constraints on the ribcage, there is an apparent disturbance of the causal relationship between neural respiratory drive and thoracic volume displacement. Such neuro-mechanical uncoupling is frequently observed in COPD patients (O'Donnell, 2001; O'Donnell *et al.*, 2007), and may be the basis for distressing respiratory sensations during exercise. A more detailed discussion of this relationship pertaining to UBE is presented below.

Finally, Chapter 6 of this thesis presented new evidence that UBE was sufficient to induce contractile fatigue of the expiratory muscles. Since diaphragm contractile function was maintained and the ventilatory demands of exercise were relatively low (53 ± 10% MVV), it was proposed that the reduction in expiratory muscle contractile function resulted from excessive loading of the abdominals during severe intensity UBE due to combined loads induced by ventilatory, postural and locomotor functions. The cellular mechanisms underpinning the observations were discussed in Chapter 6. Briefly, the reduction in $P_{ga,tw}$ following exhaustive arm-cranking at severe intensities was indicative of low-frequency fatigue of the abdominal muscles. At a cellular level, LFF may be due to a reduced Ca^{2+} secretion from SR in the sarcolemma and/or damaged fibre sarcomeres due to overextension of the muscle during concentric and eccentric contraction (Jones *et al.*, 1996). Because $P_{ga,tw}$ partially returned to baseline at 25-35 min post-exercise, the fatigue observed was likely due to the former.

In healthy participants, there may be several mechanisms by which respiratory muscle fatigue may cause exercise intolerance. An inability of the respiratory muscles to generate sufficient intra-thoracic pressures, could result in alveolar hypoventilation (Romer & Polkey, 2008) which may, in turn, compromise gas exchange efficiency. Respiratory muscle fatigue may negatively impact on exercise performance by increasing the intensity of dyspnoea (Gandevia, *et al.*, 1981; Suzuki *et al.*, 1992). This may occur due to an elevated pressure demand relative to the available pressure-generating capacity, metabolite-induced stimulation of sensitive receptors in the respiratory muscles, altered breathing patterns (i.e. increases in EELV that increase elastic loads) or altered respiratory muscle recruitment within a given respiratory muscle (Johnson, Aaron, Babcock & Dempsey, 1996). Another possible mechanism by which respiratory muscle fatigue may negatively impact on exercise performance is via the fatigue-induced metaboreflex response, which increases sympathetic vasoconstrictor outflow and reduces vascular perfusion of the limbs involved in locomotor activities (Dempsey, Romer, Rodman, Miller & Smith, 2006). This may, in turn, limit the ability of the muscle to perform work.

7-4.1 Neuromechanical Uncoupling

Exercise increases O_2 demand and, accordingly, O_2 extracted by the muscles is replenished and CO_2 and H^+ produced by the muscles eliminated to maintain homeostatic balance (Forster *et al.*, 2012). The initial response to exercise onset is a rapid (phase-I) increase in $\dot{V}_E$ that is controlled by peripheral (neural) feedback (Bell & Duffin, 2006) and arousal levels (Bell, Feenstra & Duffin, 2005). During exercise, pulmonary ventilation is likely controlled by a PCO_2-mediated influence on central and peripheral chemoreceptors (see Forster *et al.*, 2012 for review). These afferent feedback mechanisms increase descending neural signals from the respiratory centres to spinal locomotor neurons to increase $\dot{V}_E$ via an appropriate mechanical response. Furthermore, changes in $\dot{V}_E$ appear to be more sensitive to changes in PCO_2 during arm exercise than leg exercise (Takano *et al.*, 1992). In this thesis, neural respiratory drive was measured directly via respiratory muscle electromyogram, and indirectly via changes in airway pressure that resulted from contractions of the respiratory muscles.

The 'normal' healthy response to dynamic exercise is an increase in neural drive followed by an increase in mechanical ventilation that is deemed appropriate to satisfy the O_2 demand. In Chapter 5, participants exercising at higher cadences exhibited greater indices of neural respiratory drive that was likely associated with the increased static postural demands of high cadence arm-cranking. Since $\dot{V}_E$ was also elevated at high cadences, the neuro-mechanical relationship was likely preserved. Dyspnoea was also elevated at high cadences, and may relate to afferents from intercostal muscles that project to the motor-cortex and contribute to proprioception (Dodd *et al.*, 1984). By contrast, Chapter 4 identified participants who exhibited elevated neural respiratory drive during arm-cranking, i.e. increased rectus abdominis EMG activity and tidal oesophageal pressure swings, but a lower V_T at any given level of $\dot{V}_E$ compared to leg-cycling. Such a response is termed neuro-mechanical uncoupling, since there is an uncoupling of the relationship between neural drive to the respiratory muscles, and the mechanical response at the lung which is disproportionately low. Data from this thesis suggest, therefore, that UBE reduces the capacity of the respiratory system to optimally respond to increases in central neural drive. Although the extent of uncoupling is unlikely to induce ventilatory failure in healthy participants, the poor effort/displacement ratio observed during UBE may lead to the activation of central limbic structures and, therefore, form the basis for distressing respiratory sensations and elevated perceptions of dyspnoea (Mahler & O'Donnell, 2005). This may, in turn, reduce exercise tolerance (ATS, 2012). Furthermore, the greater the discrepancy between efferent drive and afferent feedback, the greater the intensity of dyspnoea (McConnell, 2013).

7-5 Functional Implications in Cardiorespiratory Disease

This thesis presents several novel findings related to UBE effects on respiratory function in healthy humans. Since individuals with cardiorespiratory disease present with breathing impairment, any activity that may further compromise respiratory function has implications for these populations. A full discussion of the present findings in the context of respiratory impairment is outside the scope of this thesis, and a brief overview is thus presented.

Upper-body exercise has been used as an assessment tool and in rehabilitation programmes for individuals with obstructive lung disease, e.g. COPD (Similowski *et al.*, 2002). Arm-cranking, specifically, is often the preferred modality in exercise-based pulmonary rehabilitation programmes due, at least in part, to the submaximal ventilatory demands of UBE that make it safer and more subjectively tolerable. In some individuals, e.g. spinal cord injury, exercise training for the upper-limbs may facilitate local adaptations to improve upper-limb function when carrying out activities of daily living. For some populations, however, prescribing UBE as an alternative to lower- or whole-body exercise training may be contraindicated.

This thesis presents new data to suggest that the additional loads placed on the thoracic muscles as a result of UBE may negatively impact on respiratory patterns, operating lung volumes, gas exchange efficiency, neuro-mechanical coupling and expiratory muscle contractile function in healthy, able-bodied participants. In such individuals that are free from cardiorespiratory disease, dynamic hyperinflation and neuro-mechanical uncoupling may reduce the functional capacity of the respiratory system, but is unlikely to cause task failure. The current findings may, however, have important implications for individuals with COPD who use UBE as a training and/or rehabilitation modality. Individuals with COPD already exhibit dynamic hyperinflation, elevated neural respiratory drive and gas exchange abnormalities during exercise as a direct result of airway and lung parenchymal processes (Al Talag & Wilcox, 2014). UBE may, therefore, exacerbate respiratory abnormalities in these populations, thereby contributing to chronic exercise intolerance. Furthermore, UBE performed by healthy participants likely results in stiffening of the ribcage and abdominal wall that may limit the expansion of V_T. In those with respiratory muscle dysfunction, however, a stiffer, less compliant ribcage may inhibit V_T expansion altogether, thus further increasing the effort/displacement ratio. Increasing f_R to satisfy ventilatory demand will also exacerbate ventilatory dead space, and negatively impact on gas exchange efficiency. It is also worthy of note that UBE is associated with lower anaerobic thresholds than LBE. When combined with observations that UBE induces higher values for $\dot{V}CO_2$ and $\dot{V}_E$ at a given $\dot{V}O_2$, this indicates greater anaerobiosis during UBE compared to LBE (Martin *et al.*, 1991).

This notion may be reinforced with observations from Chapter 4 that RER during UBE was higher, at any given $\dot{V}_E$, when compared to LBE. At any given work rate, therefore, anaerobic metabolism is likely to play a greater role in ATP production during UBE. This should be carefully considered when designing assessment strategies and pulmonary rehabilitation programmes for those with cardiorespiratory disease.

Data from Chapter 6 shows overt expiratory muscle fatigue in healthy participants in response to arm-cranking performed at a relatively modest percentage of MVV, as demonstrated by a significant reduction in expiratory muscle contractile function following magnetic nerve stimulation. Individuals with obstructive lung disease exhibit reduced functional respiratory capacity, and since inspiratory function is compromised in COPD due to increased loads, reduced mechanical advantage, and increased ventilatory requirements (McKenzie, Butler & Gandevia, 2009), they may be susceptible to fatigue. An inability to produce adequate neural drive to the respiratory muscles may lead to ventilatory failure (McKenzie *et al.*, 2009) which places the patient at a high risk of death (Budweiser *et al.*, 2008). As a result, exercise assessment and/or training modalities that increase mechanical loading of the muscles of respiration, should be avoided. Brisk ambulation (Revill, Morgan, Singh, Williams & Hardman, 1999), swimming pool-based aqua-therapy (Rae & White, 2009), and supervised cycling that emphasises steady-state aerobic exercise (Ong, Chong, Soh & Earnest, 2004) may all be appropriate.

7-6 Technical Considerations

Although every effort was made to maximise the reliability and external validity of the measures in each study, in addition to controlling external (confounding) variables, there are several considerations that should be made when interpreting the findings of this thesis in the context of wider research.

7-6.1 Participants

There are several major findings from this thesis that may have implications for upper-body exercise performance; specifically these were dynamic hyperinflation, a mismatch between neural drive and ventilatory output compared to LBE, and expiratory muscle contractile fatigue. The first major consideration is that all three experimental chapters refer to observations made in healthy but otherwise untrained male participants, observations that may not extend to trained participants or athletes. Both sprint and endurance training have been shown to induce substantial musculoskeletal adaptations, including changes in fibre-type distribution and energy metabolism (for review see Abernethy, Thayer & Taylor, 1990). Furthermore, training-induced increases in

inspiratory muscle strength are associated with fatigue resistance in humans (Romer, McConnell & Jones, 2002a; Romer, McConnell & Jones, 2002b; Verges, Lenherr, Haner, Schulz & Spengler, 2007; Verges, Renggli, Notter & Spengler, 2009). Athletes may, therefore, exhibit a reduced incidence of respiratory muscle contractile fatigue following UBE. Conversely, athletes trained in upper-body sports are capable of generating greater external power compared to untrained participants, and can achieve values for arm-crank $\dot{V}O_{2peak}$ that are substantially closer (~90%) to their cycle exercise $\dot{V}O_{2peak}$ (Cerretelli *et al.*, 1977; Seals & Mullin, 1982). Since diaphragm fatigue is thought to be associated with a high ventilatory demand (Romer & Polkey, 2008) and is reportedly greater in participants who exercise at intensities in excess of 85% $\dot{V}O_{2max}$ (Johnson *et al.*, 1993), it may be that trained participants have a greater propensity to dynamically hyperinflate during exhaustive UBE and exhibit respiratory muscle contractile fatigue following said exercise. There is preliminary data to confirm this phenomenon in an elite upper-body athlete (Tiller *et al.*, 2014). However, until studies assessing the respiratory responses to UBE are conducted more extensively in trained populations, care should be made when extrapolating the present findings.

7-6.2 Constant-Power Exercise

A second consideration is the appropriateness of the constant-power exercise test used in the assessment of respiratory muscle fatigue in Chapter 6. There may be day to day differences in participant motivation, diet, effort perceptions, and biological variability, and a learning (practice) effect of the exercise task, all of which can lead to variations in performance in consecutive measures. Furthermore, all of these confounding variables have the potential to influence the degree of measured respiratory muscle contractile fatigue. In controlling for these external factors, several methodological controls were enforced. Participants were required to give a 'maximal voluntary effort' during both constant-power trials, and verbal motivation was provided by the same researcher during both trials. Both constant-power tests were conducted at the same time of day to eliminate any influence of circadian variance, and participants were instructed to follow a similar diet and exercise plan prior to both visits. Finally, great care was made to correctly identify each participant's gas exchange threshold to ensure exercise tests were conducted at 'heavy' and 'severe' intensities (Lansley *et al.*, 2011). By accurately calculating the exercise intensity for each constant-power test, the researcher had a degree of influence over each participant's time to exhaustion, and could be confident of maximising the likelihood of inducing contractile fatigue of the respiratory muscles, should such exercise be capable of doing so. If all external variables are adequately controlled, the random error associated with such constant-power tests is as low as ~1% (Paton & Hopkins, 2001).

7-6.3 Arm-Cranking Exercise

A third consideration is that arm-cranking was selected for this thesis as the exercise mode by which all quantitative responses to UBE would be assessed. Arm-cranking, however, is not necessarily representative of all UBE. The locomotor mechanics are non-specific, and the exercise mode is not comparable with upper-limb dependent sports-specific tasks like racket sport, weight-lifting or boxing. As such, care should be taken when extrapolating the findings of this thesis to narrower contexts. However, the use of arm-cranking as the upper-limb exercise mode was carefully considered. First, stationary cycling was a natural choice for the lower-body comparison in Chapter 4 since there is likely to be a high-degree of task familiarity for cycling even in untrained participants. In order to ensure external validity of the data collected, it was important to select an upper-body exercise modality that was comparable with cycling in terms of the repetitive, cyclical nature of the task. The rise in energy expenditure during arm-cranking and leg-cycling increase linearly with work performed when expressed as increments of absolute power (Bobbert, 1959), whereas other lower-body exercise modes, e.g. treadmill walking, exhibits a non-linear increase in energy expenditure with increments of either speed or gradient. Regression gradients suggest comparable values for absolute efficiency between arm-cranking and leg-cycling (22.1 versus 20.3%, respectively; Bobbert, 1959). As such, differences in physiological function between the two modes of exercise are likely to be mechanically-mediated. Furthermore, arm-cranking provides an effective upper-body exercise stimulus without the need for sports-specific technical coaching, as would be necessary in e.g. rowing. Finally, arm-cranking has been used as a reliable means by which to assess aerobic capacity during maximal (Leicht, Sealey & Sinclair, 2009) and submaximal (Bulthuis, Drossaers-Bakker, Oosterveld, Van der Palen & Van de Laar, 2010) exercise.

7-6.4 EMG Measurements

A final technical limitation of the thesis is the ‘global’ nature of the electromyographic measurements that were made throughout. Chapters 4 and 6 used skin-surface electrodes to assess the rectus abdominis, while Chapters 5 and 6 assessed activation of the crural diaphragm using a multi-pair electrode catheter. These EMG measurements represent global activation of the muscle from the CNS, but the specific ventilatory, postural and locomotor inputs to the thoracic muscles could only be inferred by the experimental design. To the author’s knowledge, there are no techniques in use that are capable of quantifying such data during dynamic exercise, although one potential avenue of future research is discussed below. Various strategies were used to overcome this limitation. First, both EMG and intra-thoracic pressure data were recorded simultaneously in order to provide an indication of work performed by the respiratory muscles,

and ratios of pressure data, i.e. Poe/Pdi, were assessed to determine the relative contribution of the ribcage muscles to transdiaphragmatic pressure generation. Furthermore, in an effort to delineate the postural/locomotor functions of the expiratory muscles, Chapter 4 assessed these outcomes during ventilation-matched exercise of different mechanical demands. Finally, by manipulating cadence rate in Chapter 5, similar data was collected during conditions of varying postural and locomotor demand.

7-7 Recommendations for Future Research

The experimental works in this thesis provide further insight into the mechanical-ventilatory responses and consequences of UBE in healthy humans. Specifically, it has characterised the healthy respiratory mechanics of predominantly UBE, attempted to establish several mechanisms for the phenomena observed, and assessed the influence of contractile respiratory muscle fatigue in response to UBE. Based on the data presented and associated discussion, there are several avenues for further research that deserve consideration.

7-7.1 How is the exercise-induced metaboreflex response influenced by UBE?

The fatigue-induced metaboreflex response results in increased sympathetic vasoconstrictor outflow and reduced vascular perfusion of the limbs involved in locomotion. This may, in turn, limit the ability of the muscles to perform work (Romer & Polkey, 2008). During UBE, the major expiratory muscles are progressively loaded due to combined ventilatory, locomotor and postural functions. Following diaphragm postural withdrawal during dynamic exercise, the demand on the abdominals is further increased by way of compensatory static contractions in order to maintain postural stability by stiffening the lumbar spine (Hodges *et al.*, 2005). The result is contractile fatigue of the expiratory muscles. Following a reduction in contractile function, it is possible that vascular conductance of the upper-limbs may be compromised by the exercise-induced metaboreflex. There are several further queries that arise from this observation: 1) does such a reduction in upper-limb vascular conductance occur during UBE, and is there a subsequent impact on exercise tolerance? 2) it is assumed that the reduction in limb blood flow following the metaboreflex is re-directed towards the respiratory muscles, but it is unclear whether the respiratory muscle vasculature also vasoconstricts in response to global sympathetic outflow. To address this, fatiguing exercise and/or fatigue-inducing expiratory muscle loading may be conducted with simultaneous measurement of respiratory muscle blood flow; 3) if the metaboreflex response has the potential to compromise locomotor limb vascular conductance, what are the implications on the major expiratory muscles that, during activities like arm-cranking, may also be considered a locomotor muscle? If the respiratory functions of the rectus

abdominis are prioritised, as is observed with the diaphragm, then presumably blood flow to the abdominals will not be compromised. By contrast, if the locomotor functions dominate sympathetic outflow, then vascular conductance may well be reduced. Further research in this domain will contribute to our growing knowledge on the functional implications of exercise-induced respiratory muscle fatigue.

7-7.2 What is the impact of UBE on dyspnoea, and how can respiratory symptoms be reduced?

Data from this thesis show elevated central drive during UBE, coupled with low V_T. In addition, participants reported elevated dyspnoea during postural disturbances induced by high cadence arm-cranking that resulted in elevated $\dot{V}_E$. Neuro-mechanical uncoupling may form the basis for distressing respiratory sensations and elevated perceptions of dyspnoea (Mahler & O'Donnell, 2005), but breathing discomfort in response to the elevated neural drive associated with UBE was not comprehensively assessed in this thesis. Since dyspnoea may have a significant and negative impact on exercise tolerance (ATS, 2012), an assessment of dyspnoea in the context of UBE requires further study. Inspiratory effort is not synonymous with inspiratory pressure, per se. For a given tidal pressure, the perception of respiratory effort is a function of maximal inspiratory pressure, i.e. the closer the respiratory pressure is to the maximum capacity for pressure generation, the greater the perception of respiratory effort (Leblanc *et al.*, 1988). Respiratory muscle training has the potential to reduce the severity of dyspnoea in healthy participants and individuals with obstructive pulmonary disease, most likely via reductions in the level of motor outflow (McConnell & Romer, 2004). There are also recent reports that inspiratory muscle training reduced neural respiratory drive, improved symptoms of dyspnoea and increased endurance time at a given $\dot{V}_E$ in COPD patients with inspiratory muscle weakness (Langer *et al.*, 2014). Respiratory muscle training may improve inspiratory muscle strength and quality of life in patients with COPD (Weiner & McConnell, 2005; Geddes, O'Brien, Reid, Brooks & Crowe, 2008), in addition to improving athletic performance in healthy participants (Romer & McConnell, 2004). As a result, interventions to increase the maximal pressure-generating capacity of the respiratory system, and the subsequent impact on the reduction of neuro-mechanical uncoupling during UBE, may positively impact exercise tolerance in this modality. There is a paucity of data, however, on the influence of respiratory muscle training on the physiological and perceptual responses to UBE. Given the high thoracic loads associated with UBE, such an intervention may prove particularly effective in promoting exercise tolerance during upper-body modalities.

7-7.3 What are the relative contributions of ventilation and posture to respiratory muscle EMG?

Each experimental chapter in this thesis quantified respiratory muscle activation. Specifically, Chapters 1 and 3 used skin-surface electrodes to assess the rectus abdominis, while Chapters 2 and 3 assessed activation of the crural diaphragm using a multi-pair electrode catheter. These EMG measurements represent global activation of the muscle, i.e. the electrical current propagating the sarcolemma induced by ion exchanges resulting from central neural drive. An important distinction that was unable to be delineated from this body work was the relative contributions of ventilatory and postural input to the gross EMG signal. This question has been partially addressed by Hodges and Gandevia, (2000) and Hodges *et al.* (2001), who made measurements from the right costal diaphragm and transverse abdominis during rapid and repetitive arm movements using bipolar fine-wire intramuscular electrodes. They evaluated EMG signals in the frequency domain to determine the power of the signal at the frequency of either arm movement and/or respiration, and as such, determined the relative postural or respiratory neural input to the diaphragm (Hodges & Gandevia, 2000). By making similar measurements during dynamic upper- and whole-body exercise, it would be possible to directly elucidate the ventilatory and postural neural drive to the respiratory muscles during UBE. There are several problems in making these measurements during UBE. First, since the electrodes were inserted between the intercostal spaces, in close proximity to the pleaural space, fine-wire recordings from the diaphragm during dynamic UBE are contraindicated due to the risk of pneumothorax. Second, although in theory, frequency domain measurements may be possible by assessing the crural diaphragm EMG using an oesophageal catheter, readings from the costal diaphragm using skin surface electrodes are likely to be contaminated by signals from adjacent muscles. Furthermore, since the crural diaphragm is more sensitive to postural changes and CO_2 stimulation than the costal portion (Van Lunteren *et al.,* 1985) data from dynamic studies in UBE may be difficult to interpret. If safe and effective techniques can be developed to make such measurements, this may be an important avenue of research to further our understanding of respiratory muscle function during exercise.

7-7.4 To what extent do the trunk muscles support posture and locomotion during UBE?

This thesis presented a new model to conceptualise the functions of the various thoracic muscles during UBE. These functions can be loosely categorised into proactive (dynamic locomotor) and reactive (static postural) muscle contractions. The diaphragm, for example, plays an essential role in reactive postural contractions during brief, intermittent disturbances to spinal stability (Hodges & Gandevia, 2000). When the chemical drive to breathe increases during dynamic exercise,

pontomedullary input to the diaphragm is prioritised and postural drive withdrawn. As a result, diaphragm EMG and oesophageal pressure data that is recorded during exercise can be largely attributed to contractions of the diaphragm for ventilatory functions. There are reports that inspiratory drive is distributed differently across different inspiratory muscles, possibly according to their mechanical effectiveness (Butler, 2007), for example, isometric rotational tasks result in elevated activation of the parasternal intercostals (Hudson *et al.*, 2010) without concomitant activation of the diaphragm. The erector spinae also contracts phasically during rapid arm movements (Zedka and Prochazka, 1997), even during dynamic exercise when $\dot{V}_E$ increases. It is likely, therefore, that other thoracic muscles, i.e. those with less of a dominant role in producing pulmonary ventilation, contract isometrically during arm-cranking in order to aid in postural support. Further understanding the relative roles of the trunk and respiratory muscles during UBE may have functional implications for those with respiratory dysfunction and musculoskeletal injuries. A full 'thoracic muscle recruitment profile' may be developed to characterise the relative role of the trunk muscles during a range of tasks including voluntary ventilation, sports-specific movements and functional tasks including activities of daily living.

7-7.5 What is the impact of UBE on gas exchange efficiency and exercise tolerance?

In the present thesis UBE resulted in constrained V_T, increased f_R, and increased $\dot{V}_E/\dot{V}CO_2$ at any given $\dot{V}_E$. Although not directly assessed, the respiratory patterns observed likely increased the ventilation dead space volume which can negatively impact on gas exchange efficiency in several ways including alveolar-ventilation perfusion mismatching and exercise-induced arterial hypoxemia which reduce exercise performance (Dempsey & Wagner, 1999; Romer, Haverkamp, Lovering, Pegelow & Dempsey, 2006). Although maximal exercise was performed in each experimental chapter, exercise 'performance', per se, was not directly assessed. Further studies are needed, therefore, to test the hypothesis that UBE may lead to gas exchange inefficiency, thereby reducing mode-specific exercise performance. A direct comparison with the responses to LBE would provide further clarity.

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APPENDIX A

ETHICAL APPROVAL

Head of School of Sport & Education
Professor Susan Capel

Brunel UNIVERSITY WEST LONDON

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Nicholas Tiller
PhD (Sport Sciences) Student
School of Sport and Education
Brunel University

12th July 2011

Dear Nick

RE34-10 Breathing mechanics and ventilatory constraint in upper vs lower body exercise

I am writing to confirm the Research Ethics Committee of the School of Sport and Education received your application connected to the above mentioned research study. Your application has been independently reviewed to ensure it complies with the University/School Research Ethics requirements and guidelines.

The Chair, acting under delegated authority, is satisfied with the decision reached by the independent reviewers and is pleased to confirm there is no objection on ethical grounds to the proposed study.

Any changes to the protocol contained within your application and any unforeseen ethical issues which arise during the conduct of your study must be notified to the Research Ethics Committee for review.

On behalf of the Research Ethics Committee for the School of Sport and Education, I wish you every success with your study.

Yours sincerely

Dr Gary Armstrong
Chair of Research Ethics Committee
School Of Sport and Education

Head of School of Sport & Education
Professor Susan Capel

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Nicholas Tiller
PhD (Sport Sciences) Student
School of Sport and Education
Brunel University

14th November 2012

Dear Nick

RE06-12 – Effects of ribcage and abdominal stiffness on breathing mechanics during upper-body exercise.

I am writing to confirm the Research Ethics Committee of the School of Sport and Education received your application connected to the above mentioned research study. Your application has been independently reviewed to ensure it complies with the University/School Research Ethics requirements and guidelines.

The Chair, acting under delegated authority, is satisfied with the decision reached by the independent reviewers and is pleased to confirm there is no objection on ethical grounds to grant ethics approval to the proposed study.

Any changes to the protocol contained within your application and any unforeseen ethical issues which arise during the conduct of your study must be notified to the Research Ethics Committee.

On behalf of the Research Ethics Committee for the School of Sport and Education, I wish you every success with your study.

Yours sincerely

Richard Godfrey

Dr Richard Godfrey
Chair of Research Ethics Committee
School Of Sport and Education

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Nicholas Tiller
PhD (Sport Sciences) Researcher
School of Sport and Education
Brunel University

5th November 2013

Dear Nick

RE01-13 Effects of upper and lower body exercise on respiratory muscle fatigue

I am writing to confirm the Research Ethics Committee of the School of Sport and Education received your application connected to the above mentioned research study. Your application has been independently reviewed to ensure it complies with the University/School Research Ethics requirements and guidelines.

The Chair, acting under delegated authority, is satisfied with the decision reached by the independent reviewers and is pleased to confirm there is no objection on ethical grounds to grant ethics approval to the proposed study.

Any changes to the protocol contained within your application and any unforeseen ethical issues which arise during the conduct of your study must be notified to the Research Ethics Committee for review.

On behalf of the Research Ethics Committee for the School of Sport and Education, I wish you every success with your study.

Yours sincerely

Dr Richard J Godfrey
Chair of Research Ethics Committee
School Of Sport and Education

The Queen's Anniversary Prizes
2011

APPENDIX B

HEALTH QUESTIONNAIRE & INFORMED CONSENT

Brunel UNIVERSITY LONDON

PRE-PARTICIPATION HEALTH CHECK QUESTIONNAIRE

'Effects of upper- and lower-body exercise on respiratory muscle fatigue'

Health and safety within this investigation is of paramount importance. For this reason it is essential that we are aware of your current health status before you begin any testing procedures. The following questions are designed to establish whether you need to obtain medical advice before participating in this study, and whilst every care will be taken to minimise any risks associated with testing, you as an individual must know your limitations.

Participant name: …… **Date of birth:** ___/___/_____

Emergency Contact Name:…… **Emergency Contact Tel:**……

Please answer the following questions:	**YES**	**NO**
1. Has your doctor ever diagnosed a heart condition or recommend only medically supervised exercise?	☐	☐
2. Do you suffer from chest pains, heart palpitations or tightness of the chest?	☐	☐
3. Do you have known high blood pressure? If yes, please give details (i.e. medication)	☐	☐
4. Do you have known hypercholesteremia?	☐	☐
5. Do you suffer from diabetes? If yes, are you insulin dependent?	☐	☐
6. Do you suffer from any lung/chest problem, e.g., asthma, bronchitis, emphysema?	☐	☐
7. Do you suffer from epilepsy? If yes, when was the last episode?	☐	☐
8. Are you a smoker? If yes, please give number per week.	☐	☐
9. Are you allergic to local anaesthetics, latex or peanuts?	☐	☐
10. Do you have hepatitis, HIV or any blood clotting disorders?	☐	☐
11. Do you have any metallic objects or implants in your body, e.g. pacemaker, shrapnel etc?!	☐	☐
12. Do you know that you have liver disease, portal hypertension or oesophageal varices?	☐	☐

13. Please document your current weekly exercise routine;

Type of exercise (cycling, running, weight training etc)	**Number of sessions/week**	**Duration of session**

If you feel at all unwell as a result of a temporary illness (cold or fever) please inform the investigator. Please note that if your health status changes and in any way affects the answers you provided to the questions above, it is paramount that you notify the investigator immediately.

I have read and fully understand this questionnaire. I confirm that to the best of my knowledge the answers provided are correct and accurate. I am aware of no reasons why I should not participate in physical activity and I am fit and fully able to volunteer for this investigation. I understand I will be taking part at my own risk.

Participant's name & signature:_____Date:_____

Investigator's name & signature:_____Date:_____

Brunel UNIVERSITY LONDON

PRE-PARTICIPATION CHECKLIST

'Effects of upper- and lower-body exercise on respiratory muscle fatigue'

Please complete the following documents independently before participating in this research study.

	YES	NO
1. Have you read the 'Participant Information' sheet?	☐	☐
2. Have you had an opportunity to ask questions and discuss your thoughts/concerns on the study?	☐	☐
3. Did you receive satisfactory answers to your questions?	☐	☐
4. Do you understand that you will not be referred to by name in any report concerning this study?	☐	☐
6. Do you understand that you are free to withdraw from the study:		
* At any time	☐	☐
* Without reason	☐	☐
* Without subsequent penalty or prejudice	☐	☐
* Without affecting your future care	☐	☐
* Without affecting University grade	☐	☐
7. Do you agree to participate in this study?	☐	☐

Participant Signature:..... **Date:**.....

Participant Full Name (Print):.....

Witness Statement: *"I am satisfied that the above-named has given informed consent".*

Witness Signature:..... **Date**.....

Witness Full Name (Print).....

APPENDIX C

BORG'S MODIFIED CR10 SCALE

0	Nothing at all	“No P”
0.3		
0.5	Extremely weak	Just noticeable
1	Very weak	
1.5		
2	Weak	Light
2.5		
3	Moderate	
4		
5	Strong	
6		
7	Very Strong	
8		
9		
10	**Extremely Strong**	**“Max P”**
11		
↓		
●	Absolute Maximum	Highest possible

Borg CR10 Scale