

CHARACTERISATION OF
CARDIORESPIRATORY RESPONSES TO
ELECTRICALLY STIMULATED CYCLE
TRAINING IN PARAPLEGIA

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Abstract

Functional, electrically stimulated (FES) cycle training can improve the cardiorespiratory fitness of spinal cord injured (SCI) individuals, but the extent to which this can occur following high volume FES cycle endurance training is not known. The effect of training on aerobic endurance capacity, as determined by the appearance of respiratory gas exchange thresholds, is also unknown. The oxygen cost (O_2 cost) of this type of exercise is about 3.5 times higher than that of volitional cycling, but the source of this inefficiency, and of the variation between subjects, has not yet been investigated. The electrical cost of FES cycling, measured as the stimulation charge required per Watt of power produced ($stim/P^t$), has neither been calculated nor investigated before. It is also not known whether a period of FES cycling can alter the O_2 cost or the $stim/P^t$ of this unique form of exercise. Additionally, the acute metabolic responses to prolonged, high intensity FES cycling after a 12-month period of high-volume training have not yet been characterised for this subject group.

Accordingly, these parameters were investigated over the course of a 12-month home-based FES cycle training programme (up to 5 x 60 min per week) in 9 male and 2 female individuals with paraplegia. Outcomes were investigated using a novel, sensitive test bed that accounted for both internal and external power production (P^t). The test protocol permitted high resolution analyses of cycling power and metabolic thresholds, and a sensitive training dose-response analysis, to be performed for the first time in FES cycling. Efficiency estimates were calculated within a new theoretical framework that was developed for those with severe disability, and the $stim/P^t$ was determined using a novel measure designed for this study.

The current training programme resulted in significant improvements in cardiorespiratory fitness and peak cycling power, but only over the first 6 months when training was progressive. These improvements were positively related to the number of training hours completed during this time. It is not known whether the plateau in training response that was found after this time was due to a physiological limitation within the muscles, or to limitations in the current stimulation strategy and of the training protocol used.

The efficiency of FES cycling was not significantly altered by any period of training. However, the $stim/P^t$ of cycling had reduced over the first 6 months, probably as a result of a fibre hypertrophy within the stimulated motor units. The relationship that was found between variables after this time suggest that differences in the efficiency of FES cycling

between subjects and over time related primarily to the stim/P^t , which determined the number of motor units recruited per unit of power produced, rather than to metabolic changes within the muscle itself.

The aerobic gas exchange threshold (GET) was detected at an oxygen uptake (\dot{V}_{O_2}) equivalent to that normally elicited by very gentle volitional exercise, even after training. This provided metabolic evidence of anaerobic fibre recruitment from the outset, as a consequence of the non-physiological motor unit recruitment pattern normally found during FES.

The cardiorespiratory stress of training was found to be significantly higher than that elicited by the incremental work rate tests, calling into question the validity of using traditional, continuous incremental work rate tests for establishing the peak oxygen uptake ($\dot{V}_{O_{2\text{peak}}}$) of FES cycling. The respiratory exchange dynamics observed over a 60 min training session were characterised and provide a unique insight into the remarkable aerobic and anaerobic capacity of trained paralytic muscles.

For this particular highly motivated subject group, training for 60 min per day on more than 4 days of the week was demonstrated to be feasible, but not able to be sustained. Further work is therefore recommended to develop and to evaluate different stimulation patterns and parameters, loading strategies and training protocols. The aim would be to determine the optimal combination of training parameters that would maximise favourable training responses within a more viable and sustainable lower volume, training programme for this subject group.

In conclusion, the outcomes of this multi-centre study have demonstrated the clinical significance of using otherwise redundant, paralytic leg muscles to perform functional, regular physical exercise to improve cardiorespiratory and musculoskeletal health after SCI. Additionally, the significant increases in cycling power and endurance that were achieved opened up new mobility and recreational possibilities for this group of individuals. These findings highlight the clinical and social relevance of regular FES cycle training, and the importance of integrating FES cycling into the lives of those affected by SCI. The early and judicious implementation of this form of exercise is strongly recommended for the maintenance of a healthy body, wellbeing, and of an active lifestyle after SCI.

Acknowledgements

This thesis is based upon my observations and analysis of data that have been gathered during the course of an international research collaboration between the Centre for Rehabilitation Engineering, the University of Glasgow, the Queen Elizabeth National Spinal Injuries Unit, Glasgow, King's College, London and the Swiss Paraplegic Research in Nottwil. I would like to express my sincere gratitude and thanks to the teams at each centre that have given so much of their time and put such effort into gathering this data; to Tanja, Claudio, Pius and Helga in Nottwil, to Nick, Lynsey, Diane and Tony in London, to David and his staff at the spinal injuries unit in Glasgow, and to Stan, Ben, Sylvie and Henrik in Glasgow. My work was funded by the UK Engineering and Physical Sciences Research Council, and I would also like to extend my thanks to them for giving me this valuable opportunity.

Particular thanks go to Ken, my supervisor, for his encouragement, advice and support throughout this project. One particular piece of valuable advice that was given, '*carpe diem*', was delivered in the form of a verse of poetry, translated from latin:

Leuconoe, don't ask - it's dangerous to know -
 what end the gods will give me or you. Don't play with Babylonian
 fortune-telling either. Better just deal with whatever comes your way.
 Whether you'll see several more winters or whether the last one
 Jupiter gives you is the one even now pelting the rocks on the shore with the waves
 of the Tyrrhenian sea - be smart, drink your wine. Scale back your long hopes
 to a short period. While we speak, time is envious and
 is running away from us. Seize the day, trusting little in the future.

Odes 1.11, Horace.

This was well received, solid advice, even if taken just too literally at times . . .

The individuals who took part in this study devoted a large portion of their time, and that of their family's, to training and testing. Their investment in this study has been invaluable, giving us all a rare insight into the practicalities and daily challenges faced by those with a spinal cord injury, especially those who are motivated to maintain healthy levels of physical

activity. I would like to thank all of these individuals, Angela and Steven in particular, for their patience and their perseverance during this programme.

This thesis represents the culmination of three and a half years of a continual, and very precarious, life balancing act. The organisational skills that have been required to enable me to attend to this work with my full intellectual capacity, to run a home and garden, to raise a family and earn a living, is entirely due to the cooperation and concerted efforts of those at home: my three wonderful children, Jura, Angus and Fergus, and my dog, Rolo. Thank you all so much!

As a family, the resounding benefits of this *needs must* lifestyle are plainly evident; Jura has developed superb team leadership skills and has honed the art of adventurous and inventive cooking, Angus willingly (in mind sometimes more than body) hoovers, cleans and dusts, but his main asset is his skillful use of the lawnmower, strimmer and chain-saw. Fergus' capacity for log splitting and stacking is admirable and much appreciated, as is his talent for making a drama (mostly humorous) out of all aspects of daily life. Finally, the health benefits gained from having a dog with a penetrating stare that says 'its time for a run!', even when its raining, are incalculable.

The emotional strength and humour that has been needed to be able to hold onto, and enjoy the roller coaster of the last few years have come from the solid support and friendship of my three best friends Jean, Bruce and Kim. Thank you, you are real stars!

Thesis outline

- Chapter 1 The epidemiology, etiology and pathophysiology of SCI is briefly described, followed by an examination of the current general recommendations regarding regular physical activity for the maintenance or improvement in health and fitness. The exercise options and specific challenges facing those with a spinal cord injury are then discussed and this forms the motivation for this thesis.
- Chapter 2 An overview of traditional cardiorespiratory exercise stress testing is given, followed by a critical examination of the literature relating to FES cycle training and cardiorespiratory testing. The aims and objectives of the FES cycle training programme are then given based on these findings and these form the fundamentals of this thesis.
- Chapter 3 The subjects and general methods employed in the FES cycling study are detailed in full in this chapter, including details of the equipment and materials used in training and testing. A general description of the statistical analysis employed concludes this chapter.
- Chapter 4 The effects of the FES cycle training programme on peak cardiorespiratory and power capacity during and after training are presented and discussed.
- Chapter 5 The metabolic and electrical costs of stimulated work were estimated during FES cycling and the effects of training on these parameters was also investigated. Possible sources of influence on these variables were also examined and the results are given and discussed in this chapter.
- Chapter 6 The physiological basis of the metabolic threshold analysis paradigm is briefly examined. This is followed by an investigation into the existence of such thresholds during incremental FES cycling tests, and the effect of training on the appearance of these thresholds. The validity and utility of threshold intensity prescription for FES cycle training is critically discussed.
- Chapter 7 This chapter briefly outlines the principles underpinning traditional, volitional maximal aerobic capacity tests and questions their use as valid measures of the peak cardiorespiratory stress of FES cycling. This was based upon comparisons made between the

responses elicited by a traditional incremental work rate test (IWRT) and those elicited during an FES home training session (HTS).

Chapter 8 The conclusions from this thesis are drawn together and presented in this chapter.

Chapter 9 This final chapter includes a discussion of areas of interest for future research within the field of FES cycling.

Original contributions

- This thesis has made an important contribution towards the clinical uptake of regular FES exercise prescription after SCI. The cardiorespiratory and musculoskeletal stresses that can be sustained over prolonged periods by FES cycling provide compelling evidence for the substantial health benefits that can be gained by this mode of exercise alone. The strong evidence base provided here can be used for health promotion purposes, exercise training prescription, to inform future training studies, and for the encouragement of regular exercise participation throughout the entire SCI community.
- This thesis is the first to examine the cardiorespiratory adaptations to a high-volume, 12-month longitudinal FES exercise training programme. All previous studies have been clinic based and subject to time and resource availability constraints which has resulted in low training frequencies and session durations. Here, a home-based training programme was designed that allowed subjects to optimise their time management in order to maximise their training volume within the prescribed limits of the programme. This enabled a higher volume of FES training to be performed than ever before.
- A sensitive training dose-response analysis of peak power (P_{peak}^t) gains and $\dot{V}_{\text{O}_2\text{peak}}$ gains was made for the first time during an FES cycle training programme. This provided a unique insight into the dynamics of this relationship over time and to the limits of this type of training. This is the first study where each subject kept a detailed training diary over the course of the training programme and this information, combined with the high resolution power and metabolic analyses formed the basis for this analysis.
- The power and cadence controlled exercise tests used in this study, permitted high resolution respiratory gas exchange analyses to be performed for the first time in electrically stimulated (ES) exercise. This was also the first ES training study in which the raw breath by breath data were systematically and consistently edited by a computerised system prior to analysis. This avoided the relative subjectivity of manual data editing, and of data distortion that can occur when outlier values are included in the analysis, especially where the noise to signal ratio is high.
- This thesis has examined the effects of exercise training on the metabolic and electrical

costs of FES cycling for the first time. FES cycling efficiency was estimated using a recently developed theoretical framework developed for those with severe disability, and a novel measure of the electrical cost of FES cycling power production was devised and used here for first time in FES cycling.

- This thesis is the first to examine and characterise the acute cardiorespiratory responses to a 60 min FES cycle training session, conducted against a maximal resistance and at a variable cadence. This has provided a novel insight into the respiratory gas exchange dynamics and the energy metabolism of this unique exercise modality after 12 months of high-volume training. The outcomes provide strong metabolic evidence for the unique non-physiological recruitment, and training, of anaerobic muscle fibres throughout the entire FES cycle training session. Based on observations from this study, the use of traditional incremental exercise tests for $\dot{V}_{O_{2peak}}$ testing during ES exercise was called in to question.

Publications

- H.R. Berry, C. Perret, B.A. Saunders, T.H. Kakebeeke, N. De N. Donaldson, D.B. Allan and K.J. Hunt. Cardiorespiratory and power adaptations to stimulated cycle training in paraplegia. *Medicine and science in sports and exercise*, vol. 40, no. 9, pp. 1573–1580, 2008.
- K.J. Hunt, B.A. Saunders, C. Perret, H. Berry, D.B. Allan, N. Donaldson and T.H. Kakebeeke. Energetics of paraplegic cycling: a new theoretical framework and efficiency characterisation for untrained subjects. *European journal of applied physiology*, vol. 101, pp. 277–285, 2007
- H.R. Berry, T.H. Kakebeeke, N. Donaldson, D.B. Allan and K.J. Hunt. Energetics of paraplegic cycling: adaptations to 12 months of high volume training. *European journal of applied physiology*, in preparation.
- H.R. Berry, T.H. Kakebeeke, N. Donaldson, D.B. Allan and K.J. Hunt. The aerobic gas exchange threshold: a paradigm of volitional exercise? *Medicine and science in sports and exercise*, in preparation.
- H.R. Berry, T.H. Kakebeeke, N. Donaldson, D.B. Allan and K.J. Hunt. The peak cardiorespiratory stress elicited by stimulated cycle training and testing. *Medicine and science in sports and exercise*, in preparation.
- H.R. Berry, K.J. Hunt, C. Perret, N. Donaldson, T.H. Kakebeeke and D.B. Allan. Cardiorespiratory adaptations to 12 months of high volume functional electrically stimulated (FES) cycle training in paraplegic subjects. *46th International Spinal Cord Society Annual Scientific Meeting*, Reykjavik, Iceland, 27 June to 1st July, 2007. Oral presentation
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- H.R. Berry, C. Perret, K.J. Hunt, S. Grant, B. Saunders, D.B. Allan and T.H. Kakebeeke. Conventional incremental exercise test protocol underestimates peak oxygen uptake during stimulated cycle ergometry in paraplegia. *11th annual Congress of the European College of Sport Science*, Lausanne, Switzerland, 5th to 8th July, 2006. Poster presentation

Abbreviations

- ACE = Arm crank ergometry
- ACSM = American College of Sports Medicine
- ADL = Activities of daily living
- ASIA = American Spinal Injuries Association
- ATP = Adenosine triphosphate
- ATPase = An enzyme that catalyses the hydrolysis of ATP
- BDNF = Brain-derived neurotrophic factor
- Ca^{2+} = Calcium ions
- CHD = Coronary heart disease
- CNS = Central nervous system
- CO_2 = Carbon dioxide
- CSA = Cross sectional area
- CV = Coefficient of variation
- CWRT = Constant work rate test
- ES = Electrically stimulated
- FES = Functional electrical stimulation
- FG = Fast, glycolytic
- FITT = Frequency, intensity, time and type
- FOG = Fast, oxidative-glycolytic
- GET = Aerobic gas exchange threshold

- GLA = Glasgow
- H^+ = Hydrogen ions or protons
- H_2CO_3 = Carbonic acid
- Hb^- = Deoxyhaemoglobin
- HCO_3^- = Bicarbonate
- HLa = Lactic acid
- HR = Heart rate
- HR_{high} = Highest heart rate
- HR_{peak} = Peak heart rate
- HRL = Highest trainer resistance level tolerated at a cadence 50 rpm
- HTS = Home training session
- K^+ = Potassium ions
- IWRT = Incremental work rate test
- La^- = Lactate ions
- LON = London
- MET = A \dot{V}_{O_2} of about 250 mL/min for men and 200 mL/min for women
- MHC = Myosin heavy chain
- MLSS = Maximal lactate steady state
- Na^+ = Sodium ions
- $net\dot{V}_{O_2}$ = Oxygen uptake of stimulated work only
- $net\dot{V}_{O_{2peak}}$ = Peak oxygen uptake of stimulated work only
- NOT = Nottwil
- O_2 cost = Oxygen cost of work
- O_2 pulse = Oxygen pulse
- OBLA = Onset of blood lactate accumulation
- OE = olfactory epithelium

- OEC = olfactory ensheathing cells
- P = Paraplegic
- P^t = Total internal and external power output
- PO_{peak} = Peak external power output
- P^t_{peak} = Peak internal and external power output
- RC = Respiratory compensation point
- RER = Respiratory exchange ratio
- RER_{high} = Highest respiratory exchange ratio
- RER_{mean} = Mean respiratory exchange ratio
- RER_{peak} = Peak respiratory exchange ratio
- RQ = Respiratory quotient
- SCI = Spinal cord injury
- SD = Standard deviation
- SE = Standard error
- SO = Slow, oxidative
- SS = Stimulation saturation point (100% of min-max range)
- stim/P^t = The electrical cost of stimulated work
- SV = Stroke volume
- T = Tetraplegic
- $T_{\text{RER}1}$ = The time at which the RER reached a value of 1
- \dot{V}_{CO_2} = Rate of carbon dioxide output
- \dot{V}_{E} = Minute ventilation
- $\dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2}$ = Ventilatory equivalent for carbon dioxide output
- $\dot{V}_{\text{E}}/\dot{V}_{\text{O}_2}$ = Ventilatory equivalent for oxygen uptake
- \dot{V}_{O_2} = Rate of oxygen uptake
- $\dot{V}_{\text{O}_2\text{high}}$ = Highest oxygen uptake

- $\dot{V}_{O_2\max}$ = Maximum oxygen uptake
- $\dot{V}_{O_2\text{mean}}$ = Mean oxygen uptake
- $\dot{V}_{O_2\text{peak}}$ = Peak oxygen uptake
- WCE = Wheelchair ergometry
- $\Delta\dot{V}_{O_2}/\Delta P^t$ = Dynamic oxygen cost of work
- η = Total work efficiency
- τ = Time constant

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Chapter 1

Introduction

Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it.

Plato

The epidemiology, etiology and pathophysiology of SCI is briefly described here, with particular attention given to the effect of reduced neuromuscular activity on physical activity levels and physiological health and integrity. This is followed by an examination of the current general recommendations regarding regular physical activity for the maintenance or improvement in health and fitness with particular focus given to the unique challenges facing those with SCI. The development and use of FES exercise systems for the improvement of cardiorespiratory health after SCI is then discussed and forms the motivations for this thesis.

1.1 Spinal cord injury

SCI is a devastating and debilitating condition that affects most aspects of a sufferer's life. Muscular paralysis, sensory loss and homeostatic disfunction normally ensue to varying degrees and carry substantial physiological, psychological, emotional, financial and social costs [70].

Quality of life is often greatly reduced and secondary complications tend to increase morbidity and mortality. Respiratory disease, septicemia, pulmonary emboli and cardiovascular disease are the most dangerous secondary complications of SCI [47] and cardiovascular disease is now the leading cause of death post injury [126] (notwithstanding suicide in the under 25 age group within five years of injury) [48].

Urinary tract infections, decubitus ulcers (pressure sores), severe spasticity and a propensity towards chronic pain and stress also constitute major secondary complications of SCI and add to the management and care burden. Complete injury, tetraplegia (high spinal level injury), older age, concomitant illness and violent injury have been identified as

important risk factors in the development of secondary complications [47, 116].

In the more developed countries, where health expenditure per capita is up to 380 times that of less developed countries, advances in understanding and knowledge of SCI and judicious early management of injury have reduced mortality rates and the prevalence of complete spinal cord damage. Improved care and management of secondary complications has also improved life expectancy after injury to levels approaching that of the able bodied population, the prognosis being better for young patients than for older patients [47, 70].

The SCI population is nonetheless predominantly very sedentary, and this brings with it the many co-morbidities associated with inactivity including: obesity, hypertension, impaired glucose metabolism and an atherogenic lipid profile,¹ leading to diabetes mellitus and cardiovascular disease [59, 126]. Physical activity is recognised as a potent preventative and therapy for these conditions and as a tool for successful ageing in the able bodied population [115, 170]. Little has been done in terms of exercise programme development and research in an attempt to improve cardiorespiratory fitness or to mitigate the incipient age and condition related physiological and neurological decline after SCI [90, 133].

1.1.1 Epidemiology and etiology of injury

Traumatic SCI is a global phenomenon with annual reported incidences for different countries ranging from 14.5 per million people in Australia to 57.8 per million in Portugal [1]. Full worldwide epidemiological studies are scarce and most figures are estimates. It appears, however, that the incidence of SCI is higher in the developing world than the western world and etiology varies dependent on the country's socio-economic status [156].

There are an estimated 40,000 SCI individuals in the United Kingdom, with 745 new admissions to spinal injuries units in 2001. This figure includes 155 admissions due to other non-traumatic causes including cancer, infection, arthritis and inflammation of the spinal cord (the worldwide incidence is not known but thought to equal or exceed that of traumatic SCI). These figures, however, do not include spinal injury admissions to general hospitals [157]. Young healthy male individuals are most likely to suffer traumatic injury with male to female ratios of 1.6:1 in the UK [1], 8.1:1 in Zimbabwe and 10:1 in Nigeria [156]. Injury is most likely to be caused by a motor vehicle collision in countries such as France (57.9%), Portugal (57.3%) and Western Canada (54%) or by a fall in Bangladesh (63%) and Eastern Canada (47%) [1]. Figures for the United kingdom (2001) show that 45.5% of injuries occur as a result of falling and 39.2% from motor vehicle accidents [157].

Similar epidemiological features are found in nations with similar economies: age at time of injury is likely to be higher in more developed countries, perhaps due to longer life expectancies, and females are likely to be older than males at time of injury with the

¹Having a tendency toward fatty plaque or scar formation on the walls of arteries, eventually causing narrowing of the arteries or *atherosclerosis* [105].

male:female ratio also likely to be lower [1].

The site of injury is most likely to be the cervical spinal cord (between head and shoulders) in the more developed countries (United States 76%, Japan 74.3%, Western Canada 61.5% and 53% in the United Kingdom), and thoracic spinal cord (between shoulders and base of rib cage) in less developed countries (Turkey 85%, South Africa 75%, Brazil 64.9% and Bangladesh 60%) [156, 1].

The high incidence of young male sufferers in poorly developed countries adds an extra burden to the domestic financial situation, since they are often the sole earner in a household. Emergency first aid service and post-traumatic care are also likely to be insufficient in less developed countries leading to higher death rates in both the acute and the long term post-trauma stages [156].

1.1.2 Spinal injury classification

SCI affects volitional motor control, sensation and autonomic control of body systems. The extent to which this occurs is determined by the level and completeness of injury and the nerves affected. Spinal nerves are designated according to the vertebral level from which they exit: cervical (8 pairs, C1-C8, serving the muscles and glands of the neck, shoulder, arm and hand), thoracic (12 pairs, T1-T12, serving the chest and abdominal walls) lumbar (5 pairs, L1-L5, associated with the hip and leg), sacral (5 pairs, S1-S5, associated with the genitals, lower digestive tract and bladder) and coccygeal (1 pair, Co, associated with the tailbone) [176].

Trauma is classified by assessment of retained sensorimotor function and designated an associated nomenclature according to the *International Standards for Classification of Spinal Cord Injury* (revised 2002). This system, written by the Neurological Standards Committee of the American Spinal Injury Association (ASIA) is endorsed by the International Spinal Cord Society and is regarded as the definitive clinical guide to SCI classification [114].

Lesion level

Upper motor neurones consist of the long ascending and descending nerve tracts or *axons* of the spinal cord. These synapse within the central nervous system (CNS) and with lower motor neurones permitting central integration and processing of peripheral impulses. Lower motor neurones consist of a motor-sensory reflex arc, where a motor nerve root and a sensory nerve root enter, synapse within and leave the intervertebral foramen at the same spinal level (Fig. 1.1) [70, 176].

Upper motor neurone lesions cause a decentralisation of impulses, resulting in spastic paralysis with exaggerated and uninhibited sensorimotor reflexes below or *caudal* to the lesion level (see section 1.1.3). Lower motor neurone lesions result in sensorimotor decentralisation and areflexic, flaccid paralysis due to the disruption to the reflex arcs. Muscle tissue normally

Image removed due to copyright

(a) Spinal nerves passing through the vertebral foramen

Image removed due to copyright

(b) Spinal transection showing vertebral canal and nerve organisation

Figure 1.1: Thoracic level spinal vertebrae showing both somatic (spinal) and autonomic (visceral) nerves. (Adapted from [49])

innervated by the damaged segment is no longer subject to reflex contraction or neurotrophic effects,² and becomes severely atrophied. Injury to any level of the cord can result in an isolated areflexic segment within segments retaining functional reflex arcs [90].

Unless penetrated by a sharp object, or by the vertebral bone itself, the spinal cord is rarely transected (anatomical lesion). Interruption to the communications pathway is normally caused by infarction³ or mechanical deformation caused by swelling or contusion (clinical lesion). Consequently, there is a great deal of intra- and inter-individual variation in neurological completeness of injury and in sensorimotor sparing both acutely and in the long term after the injury has stabilised [70].

Plegias

Where there is any degree of sensorimotor loss or impairment in the cervical segments of the spinal cord, the resultant plegia or paralysis is termed tetraplegia (Fig. 1.2). This affects the functioning of the arms, trunk, legs and pelvic organs, but does not include damage caused by injury to peripheral nerves outwith the spinal canal or to the brachial plexus.⁴ Spinal lesion above C4 results in complete paralysis of all torso musculature where breathing is not possible without the use of a ventilator and individuals are reliant on total assistance for all activities of daily living (ADL). Lesions between C4 and T1 will result in varying degrees of shoulder and arm sensorimotor sparing, but all cervical lesions will disrupt sympathetic outflow. Autonomic control and cardiovascular homeostasis is affected by the imbalance in autonomic outflow (see Fig. 1.3) [70].

²The maintenance of neuronal integrity through axonal transport of structural elements, proteins and amino acids [50].

³The death of a small area of tissue as a result of inadequate blood supply [111].

⁴Complex network of nerves composed of the anterior branches of the lower four cervical and the first two thoracic nerves [49].

Image removed due to copyright

Figure 1.2: The vertebral canal with spinal cord and spinal nerves (numbered). (Adapted from [49])

Paraplegia refers to paralysis due to lesions in the thoracic, lumbar or sacral areas. Lesions between T1 and T4 will result in compromised upper body strength and balance commensurate with lesion level, with higher level injuries most affected. Sympathetic innervation is affected and autonomic dysreflexia or hyperreflexia is possible (see section 1.1.3). T5 to L1 injuries will also result in some upper body weakness and balance loss, the severity of which will also depend on lesion level. Autonomic cardiovascular control is however not affected. Lesions below L1 will retain full upper body strength and balance and varying degrees of lower limb function and control, also commensurate with lesion level [49] (Fig. 1.2).

Image removed due to copyright

Figure 1.3: Sympathetic and parasympathetic divisions of the autonomic (visceral) nervous system. (Adapted from [49])

Variations in neurological symptoms may prevent accurate diagnoses from being made and the neurological level of injury may not be immediately clear. In such cases, the patterns of injury are examined in combination with the neurological symptoms and the resultant conditions designated according to the area of the cord most affected, e.g. after a flexion-rotation force to the spine that results in a dislocation or compression fracture of the vertebrae, there is often ischaemia or trauma to the motor and sensory nerves below the lesion and the condition is termed *anterior cord syndrome*.

1.1.3 Pathophysiology of complete spinal cord injury

Body composition changes after SCI in response to reduced physical activity, immobilisation or disuse. The body minimises unnecessary expense on redundant body systems or systems subject to reduced stresses such as the musculoskeletal system and the cardiovascular system. This causes a reduction in metabolically active tissue and an increase in adiposity levels as energy balance becomes more difficult to maintain. In a cross sectional study of 133 SCI men, Spungen *et al.* [158] found that body composition changes were exaggerated with advancing age and resulted in adiposity levels and loss of lean body mass significantly greater than those

of an ethnicity-matched able bodied cohort. These factors, in addition to the lack of volitional control below the level of the lesion and the disruption to systemic autonomic control, provide unique challenges to the individual who wishes to maintain or improve physical fitness after SCI.

Musculoskeletal system

Muscle atrophy Skeletal muscles exhibit an activity and load dependent adaptive or *plastic* response whereby structural and metabolic proteins chronically alter their expression both qualitatively and quantitatively to meet changing demands [50, 139]. Paralyzed muscle responds to the reduced neuromuscular activity and reduced mechanical loading by reducing its protein synthesis turnover rate and increasing proteolysis (protein degradation). This leads to muscle atrophy (wasting) which is more pronounced where muscles are denervated and areflexic, and results in loss of potential muscle strength. The muscle fibres change their phenotype (structure and function) from slow, fatigue resistant and oxidative (aerobic) to fast, fatigable and glycolytic (anaerobic), which will affect their potential endurance capacity [159, 94, 139].

Osteoporosis Bone also exhibits an activity and load dependent adaptive response: bone density below the level of SCI, of the femur and tibia in particular, responds to the reduced dynamic biomechanical stress very quickly and reduces to reach a steady state after 3-8 years post injury. In a cross sectional study of eighty-nine motor complete SCI men, Eser *et al.* [51] found that bone loss was greatest in the epiphyses⁵ and was reduced by 50% in the femur and 60% in the tibia. Losses at this site were attributed to reductions in bone mineral density. Shaft bone mass loss was 35% in the femur and 25% in the tibia. Losses here were attributed to reductions in cortical wall thickness. The risk of fractures resulting is high and may influence an individual's subsequent chosen activity levels.

Spasticity Spasticity refers to involuntary, uncontrolled muscle spasms which occur as a result of uninhibited excitatory spinal reflexes resulting from nociception⁶ or by proprioception⁷. This only occurs where spinal reflex arcs are intact below the lesion level. In the absence of supraspinal input, there is no descending inhibition to minimise or prevent reflex contraction of the muscle and a spasm results [50]. Individuals with severe spasticity and an agonist/antagonist imbalance tend to develop contractures, which may cause deformity and worsen the existing levels of spasticity. Spasticity can maintain muscle

⁵The terminal portion of a long bone [105].

⁶The reception of pain or injury [105].

⁷The reception of stimuli generated from within the body such as movement, stretch or mechanical deformation [105].

bulk and improve venous return but can also seriously impact on ADLs and may increase the risk of fracture as a muscle/bone strength imbalance develops [71].

Bowel, bladder and sexual function Loss of bowel and bladder control and sexual function after SCI is probably the most devastating effect of injury. Neural control of the pelvic organs is under both somatic and autonomic control and relies on a complex integration of lumbo-sacral reflexes. Lesions occurring above the sacral spinal level will interrupt the pathways that coordinate sphincter control in both the bladder and the bowel and can cause incontinence. Ejaculatory function and spermatogenesis can also be impaired in men. Reflexes can become hyperreflexic (bladder hyperreflexia) or work out of synchrony (sphincter dyssynergia), but can be modified by volitional modulation techniques (upper motor lesion only) to give some degree of control over micturation (urination), voiding and ejaculation [121, 36].

Cardiorespiratory system

Cardiovascular control Those with lesions above T5 generally have compromised sympathetic innervation to the heart (see Fig. 1.3) and can experience diminished chronotropic and inotropic cardiac control via noradrenaline mediated mechanisms. This can result in hypotension (low blood pressure) and hypokinesia (reduced blood flow) [89], a delayed increase in cardiac output [124], a blunted blood pressure response [79, 99], cardiac output hyperkinetic to \dot{V}_{O_2} [145] or abnormal hyper or dysreflexic [4] responses to exercise (see below). After SCI, humeral (blood borne) feedback seems to be the main influence in circulatory haemodynamic (flow and pressure) control below the level of the injury [99].

The cardiovascular system loses its central and peripheral haemodynamic functional integrity and there is often a degree of circulatory insufficiency augmented by reduced venous muscle pump assisted cardiac return. The left ventricle of the myocardium (heart muscle) becomes atrophied due to decreased internal shear stresses, and peripheral capillarisation and vascular tone are reduced [82, 83, 98, 89]. In the acute stages of injury, the venous stasis that occurs as a result of lack of venous muscle pump activity, and alterations in blood clotting mechanisms predispose sufferers to deep vein thrombosis [143].

Decubitus ulcers Decubitus ulcers occur mainly over bony areas such as the ischial tuberosity, greater trochanter, and sacrum that are subject to periods of unrelieved body weight pressure. They are a result of tissue ischaemia caused by blood vessel compression during inactivity and can affect all underlying tissues depending on the severity of the condition. The ischaemic tissue gradually dies and, if left untreated, can spread and infect blood and bone [70].

Thermal control Thermoregulatory capacity is limited by impaired secretion by sweat glands and impaired haemodynamic control. This can lead to an overheating response in the upper body and a cooling of the paralysed lower body during exercise [90].

Metabolic changes Reductions in lean body mass are associated with a reduced basal metabolic rate and reductions in anabolic hormone production such as testosterone and growth hormones [15]. Increased adiposity is likely to be accompanied by insulin resistance and hyperinsulinemia is more likely to occur. Elevated blood insulin levels contribute to changes in blood lipids resulting in dislipidemia and hypertension which lead to an atherogenic lipid profile that is associated with an increased risk of coronary heart disease (CHD). The associated changes in glucose tolerance and handling result in an increased prevalence of diabetes mellitus (type 2 diabetes) [14].

Respiratory disease High lesion sufferers are at most risk of suffering respiratory disease which has a high morbidity and mortality risk. Impairment of respiratory muscles, a reduction in chest wall compliance, ineffective cough and reduced vital capacity combine to increase the risk of pneumonia via retained secretions. Those requiring ventilation may also have problems with speech production [21].

Autonomic dysreflexia In individuals with cervical cord injuries above the sympathetic outflow (see Fig. 1.3), and sometimes in individuals with high thoracic injuries (above T6), there is a disruption in the autonomic signalling response to nociception, which can result in a phenomenon known as autonomic dysreflexia. This potentially lethal condition presents as severe systemic hypertension (high blood pressure), bradycardia (slow heart rate), profuse sweating, anxiety and headache.

Intact nociceptors below the lesion level fire in response to stimuli such as bladder distention, constipation or pain. Electrically stimulated (ES) exercise (see section 1.3) has also been found to cause nociception [78]. The response is a reflex splanchnic (T5–L2) sympathetic outflow that causes vasoconstriction in the peripheral arterioles, causing an increase in systemic blood pressure [70]. In response to the increase in blood pressure, a counteractive parasympathetic response is elicited to reduce heart rate (bradycardia) and cause vasodilation in an attempt to reduce pressure. Sympathetic activity is also suppressed in a negative feedback manner, but these counteractive measures are effective only above the lesion level and therefore unable regain systemic homeostasis [4, 176].

Treatment is by removal of the precipitating cause, and if hypertension is persistent, by administration of vasodilatory drugs. Inadequate treatment can, however, lead to sensitisation where further attacks may then occur with minimal stimulus [70].

A dysreflexic response can sometimes be induced on demand and has been used as an ergogenic aid to performance in wheelchair sports. ‘Boosting’ was recognised by sports

authorities as being both extremely dangerous and unsportsmanlike and it is now banned by the International Paralympic Committee [19].

The pathophysiology of SCI and its associated psychological and sociological sequelae provide unique challenges to the individual with SCI who wishes to mitigate or indeed reverse the physiological decline that inevitably occurs as a result of their injury.

1.2 Exercise for health and fitness

In a recent review by Warburton *et al* [170], physical inactivity was identified as a modifiable risk factor for not only cardiovascular disease, but a great variety of other chronic diseases including diabetes mellitus, colon and breast cancer, obesity, hypertension, osteoporosis, osteoarthritis and depression. The mechanisms responsible for the exercise induced reductions in these health risks, appear to be due to a combination of favourable physiological adaptations including changes in body composition, lipid profile, glucose homeostasis, insulin sensitivity, central and peripheral hemodynamics, enhanced endothelial function, improved autonomic tone, reductions in blood pressure and reductions in systemic inflammation. Physical activity is also associated with reduced stress, anxiety and depression, which will impact on the prevention and management of other chronic diseases.

Physical activity leads to improvements in cardiovascular and respiratory function: maximal oxygen uptake ($\dot{V}_{O_{2max}}$) is increased as a result of both peripheral and central adaptations, and at a given sub-maximal intensity, minute ventilation is reduced and the myocardium itself works at a reduced oxygen cost. Heart rate and blood pressure are also reduced, there is an increase in skeletal muscle capillarisation, and the exercise intensity at which the threshold for blood lactate accumulation occurs is increased [6]. Nonetheless, a lack of physiological research relating to the benefits of exercise training in chronic disease conditions has recently been identified [133].

1.2.1 Exercise prescription

Background

The current recommended prescription for exercise as a preventative therapy for several primary and secondary chronic diseases comes from a review of the evidence from observational and randomised studies on the effects of physical activity on health [171]. The consensus of opinion is that an energy expenditure of about 1000 kcal (4200 kJ) per week is associated with significant health benefits, with additive benefits gained from increased levels of expenditure. This energy expenditure is approximately equivalent to walking for 1 hour on 5 days of the week. Nonetheless, physical activity does not have to be structured: energy expenditure can be accumulated by performing short 10 min bouts of any form of physical activity on most days of the week to achieve the recommended levels for health, with the greatest benefits being

gained from the least active as they become active. An increase in physical fitness, measured as a change in $\dot{V}_{O_2\max}$ of about 1 MET⁸. This equates to an increase in $\dot{V}_{O_2\max}$ of about 250 mL/min for men and 200 mL/min for women and is associated with a mortality benefit of 20%. Exercise performed at an intensity of between 3–5 METs is thought to represent the lowest intensity of work required to minimise health risks [171].

Current recommendations

Previously, recommendations for improvements in health were focused on improving cardiorespiratory fitness, body composition and strength. However, in light of the increasing body of research, and to address the needs of sedentary individuals who do not wish to participate in structured exercise programmes, the American College of Sports Medicine (ACSM) revised their physical activity recommendations. They advised that adults aged 18–65 yrs should perform either a minimum of 30 min of moderate physical activity on 5 days of the week (this can be an accumulation of 10 min periods of exercise), or 20 min of vigorous exercise on 3 days of the week. These can be combined to include 2 days of moderate exercise and 2 days of vigorous exercise per week [73]. The recommendations for older adults included similar exercise durations, but of lower intensity. Balance and flexibility exercises were also recommended for this age group [127].

Warburton *et al.* [170] formulated a general 4 strategy approach to physical activity prescription, encompassing the four modifiable components of exercise: frequency, intensity, time, type (easily remembered as FITT) designed to be adapted to the individual and to their requirements. Each strategy will fulfil the energy requirements recommended for health on its own, or in combination with each other, the time being devoted to each being dependent on the FITT combination employed, i.e. the higher the intensity of exercise, then the less time required to achieve the recommended energy expenditure. Nonetheless, lower intensity exercise may be more appropriate and acceptable for previously sedentary and unfit or for older people, where health benefits will be conferred even where there is little or no increase in fitness measured as $\dot{V}_{O_2\max}$.

The recommended types and levels of physical activity required to improve physiological well being and fitness levels over all age ranges are as follows [171]:

Low intensity (light effort) aerobic exercise

- 2-4 METs
- About 60 min per day
- Most (preferably all) days of the week

⁸1 MET is the metabolic equivalent of the body at rest which has an oxygen uptake value of 3.5 mL per kg body mass, per minute.

- Examples: weeding, strolling

Moderate intensity aerobic exercise

- 4-6 METs
- 20-60 min per day
- 3-5 days per week
- Examples: brisk walking (15-20 min per mile), dancing

High intensity aerobic exercise

- 6-8 METs
- 20-60 min per day
- 3-5 days per week
- Examples: jogging, swimming or cycling

Resistance and flexibility exercise

- 1-2 sets of 8-12 repetitions.
- 8-10 different large muscle group resistance exercises of moderate intensity (older or frail people should use 10-12 reps at lower resistance)
- 2-4 days per week
- Gentle reaching, bending and stretching exercises of the major muscle groups to improve flexibility (hold stretches for 10-30 seconds) 2-7 days per week

Each exercise should begin with a warm up to gradually raise the heart rate and body temperature and end with a cool down to return the heart rate and body temperature to normal. The recommended METs would be lower for elderly, and higher for younger adults [171].

1.2.2 Exercise and spinal cord injury

ADLs require great upper body strength, but are not normally sufficient to provide an adequate or effective cardiorespiratory stress for health benefits. This is due to the relatively small muscle mass employed, and the fatiguing nature of upper body work [183]. Arm cranking or wheelchair exercise represent two of the possible volitional exercise modalities for SCI individuals and both have been used to assess the cardiorespiratory fitness levels of

both trained and untrained SCI individuals. A true systemic $\dot{V}_{O_2\max}$ cannot be achieved with upper body exercise alone, so the term peak oxygen uptake ($\dot{V}_{O_2\text{peak}}$) is used instead (see 2.3) to reflect the peripheral limitations of this type of exercise. The risk of overuse injury and shoulder pain is also a very real issue for this population as it could seriously affect ADLs [24].

Peak exercise capacity

Table 1.1 outlines the outcomes of two studies that examined the $\dot{V}_{O_2\text{peak}}$ elicited by maximal volitional upper body exercise in SCI individuals [23, 41], and of a review of 20 wheelchair athlete physiology studies [19].

Table 1.1: $\dot{V}_{O_2\text{peak}}$ values in untrained and trained male and female tetraplegic (T) and paraplegic (P) individuals.

Study	Year	Mode	n	Plegia	$\dot{V}_{O_2\text{peak}}$ L/min male	$\dot{V}_{O_2\text{peak}}$ L/min female
Untrained						
Burkett <i>et al.</i>	1990	WCE	4	T	0.55	na
Bhambhani	2002	ACE/WCE	35	T	1.04	na
Davis & Shephard	1988	ACE	15	P	1.56	na
Burkett <i>et al.</i>	1990	WCE	12	P	1.57	0.87
Bhambhani	2002	ACE/WCE	88	P	1.75	0.99
Trained						
Bhambhani	2002	ACE/WCE	31	T	1.15	0.92
Davis & Shephard	1988	ACE	15	P	2.24	na
Burkett <i>et al.</i>	1990	WCE	4	P	2.12	na
Bhambhani	2002	ACE/WCE	226	P	2.3	1.96

Tests were performed by either arm crank exercise (ACE) or wheelchair ergometry (WCE). na, data not available. [23, 41, 19].

$\dot{V}_{O_2\text{peak}}$ measured using wheelchair ergometry was found to be significantly related to level of injury, with tetraplegics having $\dot{V}_{O_2\text{peak}}$ values lower than that of untrained female paraplegics, untrained male paraplegics and trained male paraplegics. The $\dot{V}_{O_2\text{peak}}$ for untrained and trained paraplegics were very similar for both exercise modalities across studies [23].

In a re-analysis of data from five different studies that assessed \dot{V}_{O_2} during maximal wheelchair exercise tests, it was concluded that \dot{V}_{O_2} capacity is largely determined by fixed factors such as lesion level, age and gender and to a lesser extent by changeable factors such as activity level and body mass. From this, normative values for physical capacity during

wheelchair exercise were determined, based on percentiles, where they deemed an average (40–60%) capacity for tetraplegics to be 0.8–0.96 L/min and 1.73–2.00 L/min for paraplegics. An excellent (>80%) capacity is regarded as >1.19 L/min for tetraplegics and >2.31 L/min for paraplegics [91].

A more recent review of 37 articles relating to the physical capacity of wheelchair-dependent persons with SCI found that, similar to the findings of Janssen *et al.* [91], the weighted mean $\dot{V}_{O_{2peak}}$ in tetraplegia to be 0.89 L/min and 2.10 L/min in paraplegia during wheelchair exercise tests [72]. The values given for both reviews were calculated from data taken from a wide range of subjects including sedentary and athletic individuals and those with incomplete injuries. It is, therefore, likely that these normative values slightly overestimate the physical capacity of the SCI population as a whole where a high proportion probably fall into the lower categories.

The lowest level of cardiorespiratory fitness required to reduce or minimise the health risks associated with inactivity often exceeds the peak values observed in both trained and untrained individuals with paraplegia. For untrained tetraplegics, the daily exercise intensity required to achieve and maintain the required fitness level exceeds their maximal aerobic capacity [23].

The well documented health benefits of regular physical activity to the general population are no less important for individuals with SCI where physical activity levels are likely to be much lower. Regular exercise training of the paralysed muscle mass will not only improve cardiorespiratory health and fitness, but will help to mitigate the inactivity related musculoskeletal decline that inevitably follows injury [?].

1.3 Functional Electrical Stimulation

Electrical stimulation is used therapeutically in SCI for control of spasticity, prevention of pressure sores, improving bowel and bladder control and restoring sexual function. It can also be used to temporarily restore useful function to paralysed muscle, where it can supplement or replace compromised voluntary function to permit standing and balance or allow rhythmical or cyclical exercise to be performed [?]. Used in this way it is commonly known as FES.

1.3.1 Motor unit stimulation

All of the muscle fibres within a motor unit will contract in response to a motor neurone action potential. An action potential can be achieved artificially by either implanted stimulation of the motor neurone nerve root or by transcutaneous, percutaneous or implanted stimulation of its axon [88]. During transcutaneous stimulation, an electric current is passed between pairs of bipolar surface electrodes which are placed on the skin, over the motor point of a muscle. The current creates an electrical field within an area of tissue determined by the

magnitude of the applied charge. This causes voltage gated ion channels to open across the membrane or *axolemma* of many nerve fibres causing action potentials to conduct in both an unnatural, antidromic direction (towards the soma) and a natural, orthodromic direction (towards the terminal boutons) along the nerve axon and its terminal branches [149].

Muscle groups are stimulated indirectly in this way, since the applied current depolarises the axolemma of the motor unit more readily than the muscle membrane or *sarcolemma* by a factor of about 100. This is because the axolemma has voltage gated ion channels whereas the sarcolemma has transmitter gated channels. ES is only effective in this way where the entire nerve is intact and still subject to neurotrophic factors i.e. still metabolically active [50, 176].

The motor unit

Motor units vary in size according to muscle function: muscles that are required to produce low force with fine motor control have the smallest motor units and those required to produce high force with little fine motor control have the largest. The physiological classification of human motor units is based on differences in tetanic force production and fatigue resistance, not by differences in contraction speed since no evidence of a strong relationship between force and contraction speed has been found in human motor units [50]. Large motor units tend to have a high fibre innervation ratios⁹ (up to about 1:2000) resulting in high tetanic force production but they fatigue rapidly. Small motor units tend to have low innervation ratios (as small as 1:6) which produce less force but allow fine motor control, and are fatigue resistant (Fig. 1.4). Fast and slow twitch motor units are nonetheless both found human muscle where differences in speed are seen to be due to the muscle fibre's different myosin ATPase¹⁰ enzymes and sarcoplasmic reticulum calcium release and uptake rate [139].

Image removed due to copyright

Figure 1.4: Motor units classified by size. Larger motor units tend to innervate a greater number of fibers than smaller motor units, resulting in a greater individual twitch tension production. They also have larger cell bodies and larger diameter axons (Adapted from <http://www.lib.mcg.edu>.)

Motor units also vary in characteristic according to their excitability (input resistance and rheobase), morphology and distribution of input. Excitability depends on cell morphology: large motor neurones have high cell capacitance, large soma (cell bodies), an extensive surface

⁹The number of muscle fibres innervated by each motor neurone

¹⁰An integral contractile protein enzyme that hydrolyses adenosinetriphosphate (ATP) and causes a conformational change in contractile protein shape that causes the fibres to slide past each other and contract the muscle [94].

area with numerous dendrites (areas for synaptic contact) and a large axon diameter. Under voluntary control, they are high threshold and require much greater central drive (willpower) to depolarise than smaller motor units [94].

Muscle fibre types

Within each motor unit, fibre types are classified according to their biochemical or molecular properties. Human fibres classified according to ATPase enzyme activity, and therefore contractile speed, are distinguished as type I (slow), or type IIA and type IID(x)¹¹(fast). When distinguished by a combination of ATPase, aerobic and anaerobic enzyme activity, fibres are classified as either slow twitch, oxidative (SO), fast twitch, oxidative-glycolytic (FOG) or fast twitch, glycolytic (FG). Differentiation based on myosin heavy chain isoforms have identified three different types: MHC-I, MHC-IIa and MHC-IIcx in humans. These correspond highly with the three biochemically determined types. The cost of tension production (ATP turnover rate) in fast fibres is up to four times that of slow fibres [39] and the associated oxygen cost of ATP regeneration is high. Fibres can be hybrid mixes of different fibre types along their length at any given time [139].

1.3.2 Motor unit recruitment

Voluntary motor unit recruitment normally follows an orderly progression, according to Henneman's orderly recruitment principle, from easily recruited, low threshold small units up to higher threshold large units. Because size determines the peak force of the motor unit, force is normally graded systematically in this way¹² [50]. In contrast to this, studies investigating direct stimulation of the motor nerve have observed this order to be reversed. It was observed that the larger motor units which generally have large, fast conducting axons depolarised more readily than the small diameter slow conducting axons of smaller motor units. However, transcutaneous stimulation appears to result in a more random motor unit recruitment pattern determined by charge level, the extent of axonal branching, nerve fibre geometry within the muscle, tissue impedance and motor unit type predominance [100, 53], notwithstanding the preferential recruitment of larger motor units still observed [165].

Action potentials that propagates toward the synaptic terminal will result in muscle action potentials, whereas antidromic impulses will dissipate at the soma, or possibly lead to synaptic potentiation¹³ [31]. Sensory nerves are also activated which can cause reflexive spasms, autonomic dysreflexia (see section 1.1.3) or pain responses to occur.

¹¹These fibres were previously classified as type IIB but have been renamed according to their myosin heavy chain complement [139].

¹²Motor unit recruitment is often disordered during all-out exercise or during certain pain reflex responses, where large high force motor units are selectively activated first [50].

¹³Where the SCI is partial, orthodromic impulses may cause a degree of synaptic potentiation that permits any weak residual voluntary presynaptic impulses to reach threshold level, resulting in a degree of restored voluntary movement [149].

Transcutaneous electrical stimulation appears to result in the synchronous recruitment of spatially fixed, nonspecific, *equivocally* nonselective motor units. This permits exercise training of all fibre types within the stimulated area at relatively low force levels, which is particularly useful for atrophied paralysed muscle, that consist of predominantly FG fibres [69]. Repeated stimulation of these fibres during ES exercise training has been found to cause fibre transformations towards more FOG phenotypes in humans and a reversal to SO phenotypes in animals after periods of training (see [154] and [143] for reviews).

1.4 FES exercise training

Volitional upper body exercise would appear to confer health protection only to trained wheelchair athletes with paraplegia [91]. Untrained subjects would achieve this protection only if they were to exercise regularly at maximal intensity, but this is likely to bring with it an increased risk of injury or upper limb pain from overuse [24]. Injuries sustained during wheelchair exercise will have a serious negative impact on the ease with which ADLs are carried out and therefore alternative ways to increase fitness levels have been investigated including FES exercise systems for the lower limbs.

1.4.1 FES exercise systems

It has been observed that most cardiorespiratory exercise training benefits are derived by performing rhythmic dynamic exercise utilising a large muscle mass to ensure that the cardiorespiratory system is maximally and effectively taxed [6]. Accordingly, various FES exercise systems have been developed to enable regular ES training of the paralysed muscle mass of the lower limbs, either on their own, or with upper body assistance. Walking, cycling and rowing systems have been developed with varying degrees of success, where it has been found that regular training can have therapeutic physiological benefits (see [90] for a review).

Although the power and endurance capacity of paralysed muscle is very limited, the metabolic stress of FES cycling has been found to be around 3.5 times higher than volitional cycling at the equivalent power output [98, 85]. This is particularly beneficial for attempting to achieve a sustained cardiorespiratory stress, especially where muscle power is limited. This is also especially important to those individuals with tetraplegia or other arm weakness that would limit their ability to exercise with the upper body. Very limited but clinically significant FES walking function, supported by a walking frame, is possible. However, even though a system is commercially available for functional use, the limitations and cumbersome nature of the system are such that FES walking is unlikely to be used for exercise training in the near future.

FES cycle ergometer systems, hybrid FES rowing systems¹⁴ [175] and hybrid FES cycle

¹⁴Hybrid systems combine FES lower limb exercise with voluntary upper body exercise.

systems [75] have all been studied and shown to be safe and effective for regular use in improving cardiorespiratory fitness. The most commonly studied and widely available system, FES cycling, provides a relatively simple, safe and effective cardiorespiratory exercise training modality that avoids the pain and injury risks associated with volitional upper body exercise.

1.4.2 FES cycling

FES cycling has been studied in clinical settings since the early 1980s when Petrofsky *et al.* first developed a cycling ergometer for the safe rehabilitation of spinal cord injured (SCI) patients. Technical advances in feedback control, and FES stimulation parameters have since resulted in the development of feedback control systems that permit both stationary and mobile exercise training [136, 137] and high-sensitivity testing on recumbent tricycle ergometers [86, 55].

FES tricycle ergometry has the potential to enhance quality of life by expanding mobility and recreational possibilities, in addition to mitigating the cardiorespiratory, cardiovascular and musculoskeletal decline that follows SCI. The physiological benefits of this exercise modality over those of volitional upper body exercise such as wheelchair ergometry or arm-cranking are mainly due to the greater muscle mass employed, the involvement of the venous muscular pump, and the more biomechanically effective movement patterns involved [169].

Physiological benefits

The physiological benefits reported from previous FES leg training studies have included improved lower body haemodynamic function, leading to improved tissue oxygenation; effective cardiac stress from increased pre-load/diastolic filling due to circulatory assistance by the skeletal venous muscle pump [40, 141, 154]; improved gas exchange kinetics [11]; load dependant changes in muscle morphology and metabolism [37]; enhanced lower leg bone mineral density [120, 57]; improved body composition [78] and increases in metabolically active tissue [153].

Cardiorespiratory adaptations

Studies investigating cardiorespiratory responses to training have been encouraging. Significant, but extremely variable, improvements in $\dot{V}_{O_{2peak}}$, peak (external only) power output (PO_{peak}) and aerobic endurance have been reported after progressive FES cycling training regimes ranging from only 6 weeks to 12 months.

Mean $\dot{V}_{O_{2peak}}$ values reported prior to training have ranged from only 309 mL/min [3] to up to 1295 mL/min [125] and post-training values of between 822 mL/min [144] and 2500 mL/min [138] have been reported after various periods of training. The differences may not only reflect differences in the individual responses to training, but may be due to

inconsistencies in the methods employed for training and testing and for subsequent data analysis across studies.

1.5 Conclusion

As a consequence of the physiological problems associated with SCI, many individuals become more sedentary than they were previously. This increases their risk of developing the various co-morbidities associated with inactivity, including cardiovascular disease, reduced bone density and unfavourable changes in body composition. These will have secondary implications such as an increased risk of bone fracture, decubitus ulcers, metabolic disorders, difficulty in performing ADLs and increased mortality. Increasing levels of physical activity have been shown to improve the health and mortality in previously sedentary, able bodied individuals. ES exercise, and FES cycling in particular, have been used in an attempt to improve the cardiorespiratory health of SCI individuals in clinical settings with encouraging but very variable results.

The following chapter briefly discusses cardiorespiratory exercise stress testing and analysis in the context of volitional exercise. The available literature relating to the research and use of FES cycling for improving cardiorespiratory fitness in the SCI population is then examined and discussed with particular reference to the test protocols and analysis methods employed. The key markers of cardiorespiratory fitness, normally associated with volitional exercise, are also examined and discussed in relation to FES cycling and FES cycling exercise testing.

Chapter 2

FES cycle training and testing

Physical fitness is not only one of the most important keys to a healthy body, it is the basis of dynamic and creative intellectual activity.

John Fitzgerald Kennedy

Traditional exercise stress testing is briefly described here and the underlying physiological basis for these tests and their key outcomes as markers of cardiorespiratory fitness is outlined. A critical review of the available literature pertaining to FES cycle training programmes and the reported effects of these programmes on these key markers of cardiorespiratory fitness in complete SCI individuals follows. FES cycle training programmes will be examined in the context of the traditional FITT principles of frequency, intensity, time and type of exercise. The test outcomes and the cardiorespiratory stress test protocols, data treatment and analysis methods employed will also be examined and discussed. The conclusions from this review will inform the aims and objectives of the present FES cycle training study and form the fundamentals of this thesis.

2.1 Introduction

The cardiorespiratory responses and adaptations to differing periods of FES cycle training by individuals with complete SCI have been examined and reported in the literature since the early 1980s. The criterion outcome measures chosen for these studies have been based on knowledge of those commonly used in traditional, volitional exercise tests.

To assess the effects of any exercise training programme on key markers of cardiorespiratory fitness, the criterion tests must provide accurate and reliable information. The contextual analysis of this information must be based on a sound understanding of the specific physiological responses that are elicited. Traditional cardiorespiratory stress tests have been devised and validated for use during volitional exercise, but their use and validity during FES exercise has not yet been fully investigated nor subjected to adequate critical scrutiny.

2.2 Conventional Exercise Stress Testing

Exercise stress tests and assessment during volitional exercise provide information on muscle power and endurance, cardiovascular control and cardiorespiratory fitness. Cardiovascular, ventilatory and gas exchange parameters can be used for diagnostic analysis in both clinical and research settings. They can be used to identify respiratory disorders and limitations, or to assess peak cardiorespiratory performance, or gas exchange thresholds and kinetics for fitness assessment [173]. Breath by breath respiratory measures at the mouth reflect gas exchange in the lungs with high temporal resolution and indicate the respiratory and metabolic stress for a given exercise modality and intensity of work [16].

2.2.1 Cardiorespiratory exercise stress tests

Tests can be maximal or sub-maximal, direct or indirect. Subjects are normally required to perform rhythmic dynamic whole body exercise to ensure that the cardiorespiratory system is effectively taxed at the required intensity [6]. Maximal, direct testing, which requires a high level of subject motivation and specialised equipment, is suitable only in clinical and research settings but gives a reliable and accurate measure of $\dot{V}_{O_{2max}}$. Sub-maximal tests can predict $\dot{V}_{O_{2max}}$ by using equations based on heart rate during or immediately after exercise at a given intensity, or by walking or running performance over a set distance. These tests are subject to prediction error and are normally suited to non-clinical environments, such as sports clubs and schools [115].

Breath by breath respiratory exchange data is subject to an inherent scattering of data points and to outliers caused by non-metabolic fluctuations in ventilation, especially in diseased or very unfit individuals [104]. This can make data interpretation and comparison very difficult, especially where data has not first been systematically edited to identify and exclude outlier breaths [147].

Data treatment is determined by whether the data is required to be analysed with a high degree of temporal resolution for kinetic or threshold analysis, or whether it is to be averaged for mean or peak response analysis. The use of a moving average is recommended for $\dot{V}_{O_{2max}}$ analysis, with the averaging window being determined by the level of data noise; 15 to 30-second windows may be considered adequate where data has little scatter and larger windows may be required for more noisy data. Raw, edited, but *unsmoothed* data is more appropriate for analyses that require a high temporal resolution [147].

2.2.2 Oxygen uptake capacity

The upper limit in systemic oxygen uptake, or $\dot{V}_{O_{2max}}$, has traditionally been regarded as the standard criterion indicator of cardiovascular and respiratory functional capacity and of maximal aerobic performance potential for whole body exercise [5, 173]. The $\dot{V}_{O_{2max}}$ of

an individual at any given time is exercise mode specific and can be increased by a period of training to a predominantly genetically determined ceiling level. Capacity will however diminish after a period of inactivity or bed rest [32].

\dot{V}_{O_2} will depend upon the aerobic capacity of the working muscle, and the muscle mass and fibre type employed (see section 1.3). The efficacy with which oxygen (O_2) can be delivered, extracted and utilised by the working musculature depends on the capacity and degree of functional integration between the central nervous, the cardiopulmonary, the cardiovascular, and the neuromuscular systems [150, 5, 173, 13, 123].

The potential upper limit for both systemic and peripheral $\dot{V}_{O_{2max}}$ is dependent on many interacting factors such as the extent of tissue capillarisation, cellular mitochondrial¹ density and oxidative enzyme activity in the working muscles, the myocardium and the lungs [128, 129]. It is also dependent on pulmonary diffusing capacity, cardiac output capacity and local and neural hemodynamic control [5, 13].

During maximal exercise utilising only a small muscle mass, e.g. single arm cycling, a greater proportion of cardiac output is available to this isolated area, resulting in a localised \dot{V}_{O_2} 2–3 times greater than that measured in the same muscle groups during maximal whole body exercise. This would indicate that $\dot{V}_{O_{2max}}$ is subject to a central rather than a peripheral limitation, as postulated by A.V. Hill *et al.* in the 1920s [13]. This was further explained by Noakes as the upper limit being reached in the oxidative capacity, and therefore pumping capacity, of the myocardium itself [128]. Maximal, small or isolated muscle group exercise will, however, achieve an overall lower systemic \dot{V}_{O_2} value due to the relatively low cardiorespiratory demand and the term $\dot{V}_{O_{2peak}}$ is used instead of $\dot{V}_{O_{2max}}$.

Exercise tests should be progressive and specific to the training mode used and incorporate work increments of a uniform magnitude and duration. These can be either continuous, allowing the subject to reach their maximum tolerable level within about 8 to 12 minutes, or discontinuous with several minutes of recovery between exercise bouts [22, 173].

The criteria, taken from the ACSM guidelines, for establishing $\dot{V}_{O_{2max}}$ in adult subjects [6] requires that they should:

- Reach a plateau in the \dot{V}_{O_2} /exercise intensity relationship.
- Have a final respiratory exchange ratio (RER)² of 1.15 or above (this is discussed in full in chapter 6)
- A heart rate of within 10 beats per minute of the age-related predicted maximum (estimated by subtracting subject's age from 220).
- A blood lactate concentration of 8 mmol per litre or more, 4–5 minutes post-exercise.

¹Mitochondrion are the sites of aerobic metabolism within a cell.

²The RER is the ratio of carbon dioxide output (\dot{V}_{CO_2}) to \dot{V}_{O_2} .

Day *et al.* [43] observed that a plateau in \dot{V}_{O_2} response, despite an increase in metabolic demand, was not obligatory as a definitive marker of $\dot{V}_{O_{2max}}$, since when compared to a range of progressively heavier constant load tests, similar maximal values were consistently found. This has recently been corroborated by Hawkins and colleagues [74].

If a subject terminates an exercise test before it is apparent that $\dot{V}_{O_{2max}}$ has been reached, due to factors such as lack of motivation, peripheral muscular fatigue, breathing difficulties or chest or limb pain, the term $\dot{V}_{O_{2peak}}$ is used instead of $\dot{V}_{O_{2max}}$ [173].

2.2.3 Aerobic endurance capacity

As exercise increases in intensity from light to very heavy or severe, then the proportion of the total energy produced by anaerobic respiration increases. This phenomenon permits the determination of aerobic endurance capacity from an incremental work rate exercise test, either by measuring the anaerobic metabolite lactate (La^-) in the blood, or by examining the respiratory exchange at the mouth.

The \dot{V}_{O_2} at which the anaerobic contribution to energy production first becomes measurable is regarded as the GET and demarcates the moderate and heavy work intensity domains. The \dot{V}_{O_2} at which the anaerobic energy contribution to work causes the isocapnic buffering³ capacity of the blood to become saturated signals the threshold from heavy to severe work intensity. The subsequent respiratory compensation that is made for the resulting metabolic acidosis can be observed from respiratory exchange measures and signals the threshold beyond which further work is very limited (severe to extreme exercise). This threshold is termed the respiratory compensation point (RC) [117]. Metabolic thresholds are described and discussed in full in chapter 6.

2.2.4 Metabolic gas exchange kinetics

At the onset of exercise or activity, or where exercise is increased or intensified, there is a period of metabolic adjustment during which time physiological systems adapt to meet the increased energy demands [109]. The rate of \dot{V}_{O_2} adjustment and the temporal delay in achieving a match between \dot{V}_{O_2} and O_2 requirements have been seen to reflect, equivocally, the systemic and peripheral O_2 delivery capacity, local muscular perfusion, and metabolic inertia [179]. The time constant or τ for this response has been found to be inversely proportional to fitness and cardiopulmonary health levels [109].

Ventilatory adjustments are influenced not only by changing metabolic demands, but by a complex interaction between supra-spinal (anticipatory), spinal (peripheral chemical and mechanical reflex) and humeral (chemical) stimuli. The rate of adjustment in gas exchange and ventilation (\dot{V}_E) follows a more or less exponential time course, where adjustment

³The maintenance of a constant arterial carbon dioxide (CO_2) pressure.

becomes proportionately smaller as \dot{V}_{O_2} reaches its new asymptote [162]. The responses can occur over 3 possible phases, depending on the change in exercise intensity. A full discussion on respiratory gas exchange kinetics is given in chapter 7.

In order to determine these parameters with a high degree of confidence, especially where the signal to noise ratio is low, multiple exercise transitions are normally performed and the average of these responses is used for the final analysis [101].

2.3 FES cycle training and testing

To attain true systemic $\dot{V}_{O_{2max}}$, the cardiorespiratory system must be maximally stressed by performing rhythmic dynamic exercise using as large a muscle mass as possible [6]. For SCI subjects performing FES cycling, the leg muscle mass employed is limited by stimulation charge, the degree of tissue impedance, and by the degree of muscle disuse atrophy and fibre fatigue resistance. This will limit the P_{peak}^t of the legs and the cardiorespiratory stress that can be elicited, especially prior to training.

Consequently, FES cycling cardiorespiratory stress tests will only provide an indication of the maximal oxidative capacity of the stimulated muscle mass itself, not of the systemic cardiorespiratory capacity. This is evident where volitional upper body exercise is performed in conjunction with FES cycling exercise and the combined exercise elicits a higher $\dot{V}_{O_{2peak}}$ than FES cycling alone [125].

Nonetheless, changes in FES cycling P_{peak}^t and $\dot{V}_{O_{2peak}}$ over time will provide a good indication of the training induced metabolic adaptations that can be achieved by this means alone. Tables 2.1 and 2.2 give summary accounts of the cardiorespiratory and power output values taken from previous FES cycling studies.

2.3.1 Muscle conditioning

A period of muscle conditioning is often required prior to cycle training or testing to ensure that the subjects are powerful enough to move their legs on the unloaded ergometer with enough fatigue resistance to complete the initial exercise stress tests and progress to cycle training. Prior strength training has been found to significantly increase FES cycling endurance capacity at a much greater rate than with no prior strength training [135].

Ten of the twelve cardiorespiratory training studies reviewed here included a preparatory period of muscle conditioning [3, 11, 67, 138, 142, 144] or cycling habituation [78, 80, 119, 125] prior to the initial baseline tests (Table 2.1). Of the seven studies investigating the acute cardiorespiratory responses to FES cycling, most included experienced FES cyclists [56, 64, 79, 145, 161], and one study examined the responses of anaesthetised able bodied subjects performing FES cycling [98]. The training status of one subject group was not detailed [10] (Table 2.2).

Table 2.1: A summary of cardiorespiratory and power output values taken from previous FES cycle training studies.

Study	Ref.	Plegia		Training (weeks)	Pre train		Post train	Pre train		Post train
		T	P		PO_{peak} (W)	PO_{peak} (W)		$\dot{V}O_{2\text{peak}}$ (mL/min)	$\dot{V}O_{2\text{peak}}$ (mL/min)	
Arnold <i>et al.</i>	[3]	5	7	34	0	30		309 ± 255	1016 ± 495	
Barstow <i>et al.</i>	[11]	2	7	8	9.9 ± 5.6	14.5 ± 5.6		1280 ± 310	1420 ± 340	
Faghri <i>et al.</i>	[52]	0	6	12	*0	17.1 ± 3.5		*~600	~800	
Goss <i>et al.</i>	[67]	2	3	26	?	?		793 ± 228	1013 ± 246	
Hjeltnes <i>et al.</i>	[78]	5	0	8	6	22.4 ± 2.2		¹ ~539	¹ ~924	
Hooker <i>et al.</i>	[80]	†10	†8	12	13.6 ± 0.4	19.7 ± 0.4		780 ± 10	950 ± 10	
Krauss <i>et al.</i>	[103]	1	7	6	¹ 6	¹ 14		510 ± 50	830 ± 60	
Mohr <i>et al.</i>	[119]	6	4	52	0	42		1200 ± 80	1430 ± 90	
Mutton <i>et al.</i>	[125]	2	9	~18	10.5 ± 4.8	14.4 ± 4.9		1295 ± 271	1424 ± 339	
Petrofsky&Stacy	[138]	0	8	26	0	55		?	2500 ± 200	
Pollack <i>et al.</i>	[142]	7	4	12	?	?		768 ± 148	1040 ± 128	
Ragnarsson <i>et al.</i>	[144]	12	7	12	0	~11		² 716	² 822	

Data are mean ± SD for [11, 67, 138] and mean ± SE for [52, 80, 119, 142]. The error term was not defined for [3, 78, 103, 125]. Individuals with either T, tetraplegia or P, paraplegia. PO_{peak} peak external power output, $\dot{V}O_{2\text{peak}}$ peak oxygen uptake, train training programme. 0 W is unloaded cycling. *Results are from sub-maximal tests conducted at 0 W. ¹Values are estimated from data presented in graph form. ²Mean values (no error term given) taken from arm-crank stress tests. †Individuals with incomplete lesion were included. ?Data not given.

2.3.2 Training programmes

All of the training programmes were clinic based and varied in their FITT parameters. Training frequencies ranged from 2 to 3 sessions per week (s/w) for most studies. One study included 7 training s/w over 5 days of the week: their subjects trained once per day for 3 days, and twice per day for 2 days of the week [78]. Work intensities were progressive in load (5 or 6 W increments) and normally set at the maximally tolerated external work rate for each session which ranged between 0 and 55 W. Training session times ranged from 5 to 60 minutes and comprised either interval [78, 103, 142, 144] or continuous cycle training, at pedal cadences of between 35 and 50 rpm.

2.3.3 FES systems and stimulation parameters

The most commonly used systems for training and testing have been the Regys 1 or the Ergys 1 or 2 systems⁴. These systems permit semi-recumbent FES cycling via computer controlled, sequential, surface neuromuscular stimulation. The stimulation parameters were programmed to provide monophasic rectangular wave stimulation with a maximum current of about 130 mA with a pulse duration of either 350 or 375 μs at a frequency of 30 Hz.

⁴Therapeutic Alliances Inc. 333 North Broad Street, Fairborn, OH 45324 USA.

Table 2.2: A summary of the acute cardiorespiratory and power output values taken from previous FES cycling studies.

Study	Ref.	Plegia		Test	Power (W)	\dot{V}_{O_2} (mL/min)	PO_{peak} (W)	$\dot{V}_{O_{2\text{peak}}}$ (mL/min)
		T	P					
Barstow <i>et al.</i>	[10]	0	8	I&C	0	930 ± 190	12.2 ± 5.6	1270 ± 270
Figoni <i>et al.</i>	[56]	0	13	I	-	-	15 ± 7	857 ± 355
Glaser <i>et al.</i>	[64]	9	11	I	-	-	$^1 \sim 14.1$	$^1 \sim 863$
Hooker <i>et al.</i>	[79]	0	7	C	6.1 ± 0.9	$^1 \sim 800$	-	-
Kjaer <i>et al.</i>	[98]	*	*	C	$^1 \sim 38$	1900 ± 130	-	-
Raymond <i>et al.</i>	[145]	0	6	I	-	-	9.2 ± 2.4	750 ± 110
Theisen <i>et al.</i>	[161]	0	5	S	28.2 ± 1.8	$^2 \sim 500$	-	-

Data are mean \pm SD for [10, 56, 145, 161] and mean \pm SE for [64, 79, 98]. PO_{peak} peak external power output values, $\dot{V}_{O_{2\text{peak}}}$ peak oxygen uptake. 0 W is unloaded cycling. ¹Values are estimated from data presented in graph form. ²Values as given or (\sim) estimated from steady state period of exercise during test. *Subjects were able bodied. Individuals with either T, tetraplegia or P, paraplegia. I, incremental test, C, constant work rate test and S, constant stimulation test.

The current amplitude was adjusted automatically to keep the pedal cadence within the pre-determined range of 35–50 rpm and stopped automatically if the cadence dropped below 35 rpm.

Ragnarsson *et al.* [144] used a modified Monark ergometer⁵ with a Regys 1 FES system and Petrofsky & Stacy [138] used a Monark ergometer with a custom FES system. For this system, biphasic square-wave stimulation was applied at a pulse duration of 350 μs and frequency of 35 Hz. The current was varied by adjusting the amplitude between 0–180 mA.

Theisen *et al.* [161] used a customised MOTOMed Viva cycle ergometer⁶ that was able to measure the power output during a constant stimulation test. The monophasic stimulation was applied at a pulse duration of 250 μs and a frequency of 35 Hz with the amplitude increased to a maximum of 120–140 mA.

2.3.4 Exercise stress testing

Incremental work rate tests Most of the incremental FES cycling stress tests have consisted of either 3 or 5-min stages of exercise performed either continuously or with 3–5 min of passive recovery and/or rest between each. A test protocol consisting of 12 min discontinuous stages (over 2 test sessions with at least 2 days separating each) was used in one study for $\dot{V}_{O_{2\text{peak}}}$ testing, where outcome variables were measured once a response “steady state” had been reached [145]. Work rate increments have typically been of 6.1 W ($\frac{1}{8}$ kp at a cadence of 50 rpm). For one study, the rate of increase in work rate was varied

⁵Grimaldi Industri AB, Hovslagargatan 5B, 2nd fl., SE-111 48 Stockholm, Sweden.

⁶RECK-Technik GmbH & Co. KG Reckstrasse 1-4 88422 Betzenweiler, Germany

according to the subject but the actual protocol details were not provided [119].

Constant work rate tests Barstow *et al* [10] tested subjects over “at least” 10 min of unloaded cycling and for one study, constant work rate responses were assessed from submaximal 12 min exercise stages that formed part of a discontinuous PO_{peak} test to determine steady state values [145].

Respiratory gas exchange A range of breath by breath metabolic cart systems were used to assess cardiorespiratory parameter outcomes. For all but one of the studies reviewed here [10], there was no information given regarding data treatment prior to analysis, such as the removal of outlying data. There was no information given regarding data averaging for 11 of the studies but where this information was noted, the raw data were automatically averaged by the metabolic system over either a 15, 20 or 30-second window. Peak values were given as the absolute highest value measured during the final exercise stage [119], or as the average of the last two 15, 20 or 30-min mean values.

Steady state exercise values were given as the average of the last 2 min of each 12 min exercise stage [145], the average of the last min of each of the incremental 4-min [138] or 5-min stages [56, 64], or not explicitly stated [10].

These methods could lead to erroneous estimates of mean or peak values where there is likely to be some distortion from unedited outlier values, especially where the noise to signal ratio is high.

2.3.5 Statistical analysis

Data has been subject to parametric and non-parametric analysis for testing the effects of training on the various outcome parameters. Five of the studies reviewed here used a conventional repeated measures ANOVA for their analysis [11, 52, 103, 142, 80] with only one stating the factor levels used [103]. There can be problems using such methods for time series analysis where data groups are, inherently, not independent of each other or where individuals respond differently to the intervention [68, 81]. Other suitable parametric time series analysis that circumvent these problems include multivariate ANOVA, adjusted univariate ANOVA, mixed modelling or simple paired *t*-tests [81] and three of the studies here used paired *t*-tests for analysis [3, 67, 145]. One study erroneously used paired *t*-tests to compare differences between independent groups of subjects under study [64], and two studies wrongly used independent *t*-tests for comparisons of the same subject groups over time [56, 138]. Additionally, it is not known whether the *t*-tests used in each study were one or two tailed. Although all studies set the level of significance to $P \leq 0.05$, it is difficult to compare effects of these training programmes on the basis of their statistical outcomes.

2.4 Acute and trained responses to FES cycling

2.4.1 Peak power output

Able-bodied FES cycling Kjaer *et al.* found that anaesthetised healthy male subjects were able to maintain a pedalling cadence of 35–50 rpm for about 23 min during an FES cycling trial. Resistance and stimulation were applied gradually over the first 15 min to allow the power to increase from ~ 20 W to ~ 38 W (previously determined sustainable power output). Stimulation and Power were then held constant until fatigue caused the cadence to reduce to below 35 rpm, when stimulation was automatically stopped [98] (Table 2.2). Considering that these subjects were able bodied and of normal muscle mass, then it would appear that this is likely to be the highest sustainable power output that can be expected with FES cycling by SCI individuals. However, it is unknown whether a period of FES cycle training would enable these able bodied subjects to increase their FES cycling power output by any degree.

Pre-training muscle conditioning Prior muscle conditioning appeared to have given individuals a large advantage in terms PO_{peak} production for some studies but not for others; pre-training PO_{peak} values ranged from unloaded cycling, or 0 W, to ~ 14 W. It is likely that the high mean baseline PO_{peak} value recorded by Hooker *et al.* [80] is due to the inclusion of incomplete lesion subjects in their study group. Their pre-training value was not dissimilar to the post-training values recorded by other studies after 6, 8 and 18 months of training (Table 2.1).

Highest measured work rates Considering the results presented by Kjaer *et al.* [98] (Table 2.2), then it seems quite remarkable that Petrofsky & Stacy found that all 8 of their paraplegic subjects could cycle at 40 W for 30 min after 3 months of training from an initial cycling capacity of only 8 min at 0 W. After a further 3 months of training all subjects were able to cycle at 55 W for 30 min (Table 2.1). It should be noted that this was the only study where the subjects trained for prolonged, 60 min sessions. This remarkable accomplishment has, nonetheless, not been replicated by any other FES study to date.

Most of the significant training gains achieved during the 52 weeks study by Mohr *et al.* [119] were reported to have occurred within the first 6 months of training. After 52 weeks of training, the highest individual peak training work rate that could be sustained by any individual was 42 W, which could be tolerated for 7 min only. One subject still cycled mostly at 0 W, three at 6 W and three at 18 W during training sessions.

In the only 2 studies where it was possible to calculate the coefficient of variation (CV) in PO_{peak} [11, 80], it was found to be 57% and 53% prior to FES training and 39% and 37% after training respectively. This illustrates the degree of inhomogeneity in this particular

population, making generalisations in outcome difficult if not invalid, especially where studies include small numbers of subjects [11], or a mix of partial and complete lesion subjects [80].

Gains in PO_{peak} relative to training duration It is difficult to find any correlation between training FITT parameters and PO_{peak} outcomes. However, when the mean improvement in PO_{peak} is expressed as gains in power per week of FES training completed (W/w), then it appears that session duration and training frequency were the most important factors for PO_{peak} gains: the highest gain of 2.12 W/w [138] was achieved over 26 weeks of prolonged (60 min per session) training of unknown frequency. The next highest gain of 2.05 W/w was attained after 8 weeks of intensive (7 s/w) training [78]. Interestingly, the studies that reported the highest pre-training PO_{peak} values also recorded the lowest improvements in PO_{peak} after training: gains of only 0.21 W/w [125], 0.5 W/w [80] and 0.58 W/w [11], were achieved over 2–3 s/w of 30 min training over \sim 18, 12 and 8 weeks respectively. This suggests that most of their gains in leg power were achieved during the cycling habituation or muscle conditioning phases prior to baseline tests being performed.

The power response to constant stimulation There has been only one study to date that has investigated the power response to constant stimulation, FES cycling over a prolonged 40 min session [161] (see Table 2.2). Stimulation was ramped up to its maximum permitted level over the first 5 min of exercise and held constant thereafter. Power output responded by rising rapidly to reach a peak after 2 min. It then dropped sharply over the next 4 min, followed by a slow recovery to reach another lower peak value by 20 min of exercise (information was not given regarding whether the power response was due to changes in pedal force or in pedalling cadence which ranged from 35–50 rpm). This pattern of response is very similar to that found during 3-min volitional all-out cycling tests [166], where power was observed to rise sharply from the outset and then fall rapidly to reach, and then plateau at, the critical power point⁷. The notable difference between the two tests is that power tends not to recover at any point during an all-out volitional cycling test and the responses occur over only 3 min of exercise. This led the authors to question the notion of ‘steady state’ during FES cycling.

2.4.2 Peak oxygen uptake

For two of the studies, the low baseline $\dot{V}_{O_{2\text{peak}}}$ values of \sim 309 mL/min [3] and \sim 510 mL/min [103] are most likely to have reflected an early termination of the exercise test due to low muscle power and rapid muscular fatigue, since the tests were performed prior to any prior muscle conditioning or cycling habituation.

⁷The maximum sustainable (aerobic) power level

$\dot{V}_{O_2\text{peak}}$ values The highest and quite remarkable post-training mean value of ~ 2500 mL/min was recorded for 8 subjects by the study that also had the highest absolute PO_{peak} and gains in PO_{peak} per week of training, but since pre-training $\dot{V}_{O_2\text{peak}}$ values were not given, it is difficult to gauge the level of improvement that occurred over time [138]. This mean peak value, which has not since been replicated, is substantially higher than the ~ 1900 mL/min reported for 8 able bodied FES cyclists with no known cardiovascular or muscular limitations [98].

The next highest mean $\dot{V}_{O_2\text{peak}}$ value reported in the literature of 1430 mL/min was subject to a large CV of 63% [119]. This may be, in part, due to the data analysis methods adopted by Mohr *et al.*, rather than merely to the inhomogeneity of subject group responses; they took the highest \dot{V}_{O_2} value recorded during the last 2 minutes of the test as $\dot{V}_{O_2\text{peak}}$ and it appears that these values were absolute, unedited values.

Gains in $\dot{V}_{O_2\text{peak}}$ relative to training duration Arnold *et al.* [3] achieved a mean improvement in PO_{peak} of only 0.88 W/w but saw the greatest absolute and relative improvements in $\dot{V}_{O_2\text{peak}}$ of 707 mL/min and 229% respectively. However, when this improvement is calculated per training week completed (mL/w), it equates to only 21 mL/w, which was not the highest gain achieved over the studies reviewed here. The highest gains, achieved over the shortest training periods, were 53 mL/w [103] and 48 mL/w [78]. These studies reported relatively low post-training $\dot{V}_{O_2\text{peak}}$ values, but two of the four highest W/w values (1.33 W/w and 2.05 W/w respectively).

Accordingly, the high absolute improvement, recorded by Arnold *et al.*, appears more likely to be due to the very low, pre-conditioning baseline values, rather than to superior training gains, since mL/w gains were not the highest calculated across studies.

Pre-test training status The post-training $\dot{V}_{O_2\text{peak}}$ values recorded by three of the studies of about 800–830 mL/min [52, 103, 144] were much lower than three of the initial baseline values of around 1200–1295 mL/min recorded in other studies [119, 11, 125]. This illustrates the difficulty in comparing $\dot{V}_{O_2\text{peak}}$ or the absolute and relative improvements in $\dot{V}_{O_2\text{peak}}$ after training, to assess the performance merits of any particular training protocol or programme. This is especially true where baseline values are measured after varying periods of different types of muscle training or cycle habituation.

Where baseline values were given after a period of muscle conditioning or cycle habituation, it appears that the weekly gains in $\dot{V}_{O_2\text{peak}}$ diminished with the length of the training programme. The greatest gains were found in studies of between 6 and 12 weeks (14 mL/w–53 mL/w) and the lowest in studies of between 18 and 52 weeks (6 mL/w–9 mL/w). This would indicate a limitation in peripheral metabolic adaptations over time.

2.4.3 Cycling endurance capacity

Continuous pedalling capacity Cycling endurance capacity has been investigated in terms of continuous pedalling duration and sustainable power output and not by metabolic threshold analysis. This is because the exercise test bed previously available to researchers in the field of ES exercise has lacked the measurement sensitivity required for a valid gas exchange threshold analysis.

In the first study to examine endurance capacity in terms of single bout duration allowed to extend beyond 30 min, it was found that bouts of cycling could be extended to a rather remarkable 150 min after just 6 weeks of cycle training, providing that there had been an initial 6 week period of prior muscle conditioning [135]. This indicates a very rapid and positive adaptation to exercise.

Anaerobic contribution to work The acute physiological responses to constant load FES cycling have been examined during bouts of continuous pedalling for periods of only 4 minutes [138] to periods of up to 40 min [161]. During the first 8 minutes of a 40 min test, where stimulation was ramped up to its maximum level over the first 5 minutes, the RER was seen to rise rapidly, reaching a peak of 1.3. It then dropped steadily over the following 30 minutes of exercise, to reach 0.9 by the end of exercise. This RER response occurred as \dot{V}_{O_2} increased steadily from ~ 200 mL/min to ~ 480 mL/min [161]. Since the power output also rose to its peak during this time, the response indicates a large anaerobic component to the energy production from the outset, consistent with the non-physiological muscle recruitment found during ES exercise (see section 1.3.2).

When comparing peak La^- accumulation and RER during FES leg cycling to that during arm ergometry, Hjeltnes *et al.* [78] found La^- accumulation to be higher (7 ± 7 vs. 4 ± 7 mmol/L) and to rise at a faster rate during FES cycling, but RER values not to be significantly different between groups (1.25 ± 0.7 vs. 1.05 ± 0.7). Over 52 weeks of FES cycle training, one study found La^- values to be high and unchanged after training (9 ± 10 vs. 12 ± 10 mmol/L) but the recorded RER values were disproportionately low and varied between 0.9 and 1.3 between subjects, but were most often below 1 [119].

Pollack *et al.* considered that since fatigue occurred in all of their subjects as RER reached unity, then this was an indicator that the anaerobic threshold had been reached and that this was a limiting factor for dynamic exercise in SCI [142]. Since this group also found $\dot{V}_{O_{2peak}}$ to have increased after training, then it would appear that the anaerobic threshold, as defined by this group, was also delayed as a result of training.

For two studies [11, 52], the RER during an unloaded cycling test exceeded unity both before and after 8 and 12 weeks of training. After 12 weeks of training, however, the RER was found to have significantly reduced (1.15 pre vs. 1.06 post) [11]. It is interesting that such high RER values were found at such low work rates, especially when peak RER values

have previously been reported to be as low as 0.89 after 6 months of FES cycle training [3].

RER fluctuations over time It is clear from the study by Theisen *et al.* [161] that the RER response to stimulation and to prolonged exercise is very dynamic; RER was measured as 1.3 with a \dot{V}_{O_2} of 800 mL/min after 8 min of exercise and as 0.9 with a \dot{V}_{O_2} of 990 mL/min after 38 min. Accordingly, it would appear that the time that the RER is assessed during a test is very important when making direct comparisons across studies. RER values will also depend on the degree of substrate depletion,⁸ and muscle oxidative potential. This may explain the disparity in RER values at a wide range of \dot{V}_{O_2} values found across studies, and the apparent mismatch between La^- values also observed.

2.4.4 Oxygen uptake kinetics

The relatively slow \dot{V}_{O_2} kinetics observed during FES cycling exercise have been attributed to muscle atrophy and deconditioning rather than to impaired autonomic control. Barstow *et al.* examined ventilatory, \dot{V}_{O_2} and heart rate responses to volitional upper body exercise and to FES cycling in the same individuals, where they found normal heart rate and ventilation kinetics for the voluntary exercise, but not for the electrically induced exercise [10]. Nonetheless, gas exchange kinetics have been found to become significantly faster after 8 weeks of training and these changes did not correlate to changes in $\dot{V}_{O_{2peak}}$, suggesting that different mechanisms were responsible for these improvements [11].

2.4.5 Cardiovascular responses

The cardiovascular responses to exercise such as heart rate, blood pressure and cardiac output have been investigated and found to be affected by autonomic system dysfunction, the degree to which this occurs is dependent on lesion level. SCI can cause severe disruption to, or loss of, the neural feed forward and feedback mechanisms responsible for precise cardiovascular control [98, 45].

Ragnarsson *et al.* failed to observe any detrimental effects as a result of compromised haemodynamic control, either acutely or after a period of FES cycle training [144]. On the contrary, this form of exercise has been seen to lead to cardiovascular and circulatory improvements, both acutely [40, 145] and after training [140, 60].

2.4.6 Efficiency

FES cycling is an *expensive* mode of exercise as it provides a relatively high metabolic stress at very low work rates. Glaser *et al.* found that, regardless of the precise definition or

⁸As glucose levels become depleted during prolonged exercise, then proportionately more energy is produced from fat and protein. This will result in a reduction in the RER value [115].

calculation, the efficiency of FES cycling is substantially lower than volitional cycling (2–14% vs. 4–34%) [64]. Efficiency during FES cycling has recently been calculated by a new method, appropriate for untrained subjects with severe physical impairment, where efficiency was estimated to be $7.8 \pm 2.1\%$ (means \pm SD) for 10 subjects. The corresponding oxygen cost, at 38.8 ± 13.9 mL/min/W was very variable and about 3.5 times higher than that normally measured during volitional cycling [85]. Additionally, healthy, anaesthetised, able bodied individuals were observed to perform FES cycling at a similar absolute work rate and with similar efficiency to untrained SCI individuals with severe muscle atrophy [98].

The electrical cost of work The mean electrical charge rate of stimulated work at a given power output was calculated for one subject in a recent study that investigated the energetics of FES cycling over periods of 5 min with two different stimulation patterns [84]. The investigators observed that there was a significant difference in the electrical and metabolic costs of power production between each of the muscle stimulation patterns for that subject. It would therefore appear that the stimulation paradigm itself is likely to have a substantial impact on the efficiency of FES cycling.

2.5 Aims and Objectives

For FES cycling to become successfully utilised as an exercise tool for improving health after SCI, the metabolic stress of cycling needs to be optimised to allow the cardiorespiratory system to become adequately and effectively stressed for the required duration. The magnitude and extent of physiological adaptation required to impact on these parameters will depend on many factors including level and type of injury, time since injury [29] which will impact on the degree of muscle disuse atrophy [7]; bone demineralisation and therefore fracture resistance [182]; fibre type transformation and metabolic adaptation, which will affect the fatigability of the muscle [139]. These factors are also compounded by hormonal influence and by individual differences in training response [115]. Outcomes, as for able bodied individuals, will also depend on the FITT parameters chosen for training [171].

The efficacy with which previous FES cycling training programmes have achieved improvements in cardiorespiratory and musculoskeletal health is equivocal, and the practical extent to which this can be achieved in a home-based setting is unknown. It is not clear whether the key markers of cardiopulmonary fitness, attained by tests designed for volitional exercise are relevant to the SCI population or to this unique exercise modality.

Accordingly, this thesis examined and characterised the cardiorespiratory and power responses to 12 months of high-volume, home-based FES cycle training. A novel, sensitive test bed and novel protocols were used for exercise testing and outcomes were systematically and consistently analysed. Outcome measures were critically evaluated for their utility in

determining key markers of adaptation to this unique type of exercise training.

2.5.1 The training programme

A brief overview of the FES cycle training programme is given here and full details of the methods employed are given in chapter 3.

Subjects A multi-centre training programme was undertaken to enable sufficient numbers of subjects to participate in this study. Due to the complex pathophysiology of SCI, only those with complete thoracic lesion injuries were chosen to participate. This was to minimise the possible effects of autonomic disruption during exercise and reduce the level of confounding variability on study outcomes, thereby improving the statistical power of analysis.

To ensure that leg muscle atrophy was in a steady state, the subjects were required to be at least 2 years post-injury. Additionally, distal tibia and femur trabecular bone densities were required to be greater than 40 mg/cm^{-3} .⁹ to minimise the possibility of muscle contraction induced fractions.

Pre-training muscle conditioning Leg muscle strength training prior to starting an FES cycle training programme has been observed to be beneficial in terms of subsequent gains in FES cycling endurance capacity. Accordingly, to ensure that all subjects had sufficient fatigue resistance to complete the first 8–12 min tests, a period of muscle conditioning was performed prior to commencing the FES cycle training programme.

FES training FITT principles Exercise prescription for health related fitness in able bodied individuals is based on the manipulation of FITT principles [171]. Exercise intensity is normally described as either light, moderate, heavy, severe or extreme. These intensity domains are determined by the level of cardiorespiratory stress elicited during exercise, which is determined by the actual and associated metabolic costs of this work (this is discussed in full in chapter 7). Accordingly, these traditional work intensity designations may not be appropriate for FES exercise prescription, where a relatively small peripheral muscle mass is maximally stimulated to contract at its maximum capacity against a maximally tolerated external resistance (severe or extreme muscular work) over prolonged periods. The La^- and RER values are also consistent with severe or extreme intensity exercise, but the \dot{V}_{O_2} values are normally only associated with exercise in the light to moderate work domains.

Since FES cycling is normally performed at 100% of the permitted min-max stimulation intensity and at a maximally tolerated pedalling resistance, then training frequency, time (duration) and type need to be manipulated to maximise the acute and chronic cardiorespiratory stress. Training can be continuous or discontinuous (interval training) in

⁹bone density as measured by peripheral Quantitative Computed Tomography

nature, but should be performed for between 20 and 60 min on 2 to 5 days (\dot{V}_{O_2} intensity dependent) of the week to comply with the current recommended physical activity levels [171, 73]. The $\dot{V}_{O_{2peak}}$ values that have been recorded in the literature suggest that sufficient cardiorespiratory stress can be elicited throughout a 30 to 60 minute cycling session to confer important cardiorespiratory health benefits. Considering that prolonged FES cycling is possible [135] and appears to be safe, this study aimed to increase cycling endurance to periods of up to 60 minutes at a maximally tolerated work rate.

Training volume There appears to be no information available regarding the optimal FES cycle training volume required to elicit maximal health or fitness related gains. However, it appears that high-volume training is likely to achieve the greatest gains [78]. The present 52 week study was designed to maximise training within a practical and achievable progressive, high training volume programme. This was designed to lead to a final training volume of 300 min per week after 16 weeks, comprising of 5 days of training per week, for up to 60 min per session. A home-based exercise programme was chosen to enable subjects to optimise their time management and maximise the training programme within the prescribed parameters. Nonetheless, due to certain inevitable circumstances, it proved difficult for all subjects to adhere strictly to the prescribed frequency and overall duration of training. Each subject completed a weekly training diary for each home training sessions (HTS) and this permitted a sensitive dose-response analysis to be performed from which the training frequency and duration for maximum improvements in power and fitness could be determined.

2.5.2 Peak FES cycling capacity

All of the FES cycling studies reviewed here used relatively large power increments in their exercise tests due to the experimental test bed that was available to them. This resulted in a lack of measurement sensitivity and an inability to detect small improvements in power over time. This study used a recently developed test bed and protocol that permitted the continuous incremental application of arbitrarily small work rates during an IWRT. This allowed the precise and consistent determination of peak cycling capacity across subjects and over time.

The raw breath by breath data were systematically and consistently edited by a computerised system prior to analysis. This avoided the the relative subjectivity of manual data editing, and of data distortion that can occur with unedited outlier values, especially where the noise to signal ration is high. $\dot{V}_{O_{2peak}}$ values were chosen as the average over a 60 s window to account for the relatively high data noise to signal ratio. This is, however, likely to result in $\dot{V}_{O_{2peak}}$ values lower than those reported in previous studies where $\dot{V}_{O_{2peak}}$ values were calculated from raw, unedited data, averaged over only 15–30 s [147].

The test protocols also permitted a sensitive training dose-response analysis and a precise

metabolic threshold analysis to be performed for the first time in FES cycling.

2.5.3 Energetics of FES cycling

FES cycling power is very low and the associated metabolic cost of this work is relatively high. The associated electrical (stimulation) cost of producing each W of power has not yet been examined between SCI individuals or over time. In light of the findings to date, it appears that the inefficiency of FES cycling is not the result of the chronic effects of SCI, such as metabolic and haemodynamic alterations and muscle fibre transformation towards a fatigable FG phenotype, but due to the stimulation paradigm employed. Nonetheless, there have been no studies to date to examine the possible effect of periods of FES cycle training on the metabolic or the stimulation costs of FES cycling. Accordingly, it was decided to examine these parameters during a constant work rate test (CWRT), over the course of the 12 month training programme. Efficiency values were estimated using measures appropriate for subjects with severe physical impairment [85], and the electrical cost of power production was calculated using a novel measure, based on the stimulation charge rate [84], that gave the total cost of stimulation for both legs, per minute, relative to each Watt of power produced.

2.5.4 Gas exchange threshold analysis

There have been no studies to date to investigate the existence of, or change in metabolic gas exchange thresholds during incremental work rate FES cycling. The test protocols used in this study enabled such an analysis to be performed, accordingly, a traditional V-slope analysis [17] of respiratory gas exchange was employed for the first time during an FES cycling study.

2.5.5 The cardiorespiratory responses to prolonged FES cycling

Only one study to date [161] has observed the power and \dot{V}_{O_2} response to prolonged (40 min) maximally stimulated FES cycling, nonetheless the cyclists were not pedalling against an imposed external load (other than the unloaded pedal friction). It was decided to periodically monitor the cardiorespiratory responses during the HTSs, conducted against a maximally tolerated external resistance at maximal stimulation, in an attempt to provide a better insight into the physiological responses to FES cycling endurance exercise. During the final week of the training programme, the cardiorespiratory responses elicited by a HTS were compared to those elicited by the final IWRT to determine the training session work intensity relative to $\dot{V}_{O_{2peak}}$.

2.6 Conclusion

In summary, this project was designed to:

1. Implement, monitor and assess a progressive, intensive home-based, 52 week FES cycle training programme for up to 15 thoracic lesion paraplegic individuals.
2. Measure and quantify the effects of training on peak cycling power output and various markers of cardiorespiratory fitness before and after 12, 26, 39 and 52 weeks of training using a novel, sensitive, test bed and test protocol.
3. Examine and quantify the stimulation cost of work over the training period and examine the energetic and metabolic adaptations to training within a new theoretical framework that accounts for both the useful internal and external work.
4. Perform respiratory gas exchange threshold analyses during incremental work rate FES cycle tests and examine their relevance within the framework of the volitional exercise metabolic threshold paradigm.
5. Examine and characterise the acute cardiorespiratory response to prolonged FES cycle training and determine the relative work intensity as a percentage of $\dot{V}_{O_{2peak}}$.

Chapter 3

Cycle training project: methods

Traditional scientific method has always been at the very best, 20 - 20 hindsight. It's good for seeing where you've been. It's good for testing the truth of what you think you know, but it can't tell you where you ought to go.

Robert M. Pirsig

The subjects and general methods employed in the FES cycling study are detailed in full in this chapter. Details are given of the equipment and materials used in training and testing and the protocols for the pre-training muscle conditioning phase and for the FES cycling training phase. The cardiorespiratory tests are also fully described. Calculations and analyses specific to a particular chapter topic are detailed in each chapter as appropriate. A general description of the statistical analysis employed concludes this chapter.

3.1 Preparation for Training

3.1.1 Subjects

12 individuals with SCI (2 female and 10 male), all of whom were motor and sensory complete lesion grade A on the ASIA impairment scale were recruited via the Queen Elizabeth National Spinal Injuries Unit, Glasgow (GLA), Swiss Paraplegic Research, Nottwil (NOT), and King's College London (LON) (see Table 3.1 for full subject details). Each subject gave their written informed consent to participate in the study which was approved by their respective centre's ethics committee: the ethics committees of the Southern General Hospital and of the Faculty of Biomedical and Life Sciences at the University of Glasgow (GLA); the ethics commission of Kanton Luzern (NOT); and the research ethics committee of Kings College Hospital (LON).

Subjects had no previous experience of stimulated leg cycling and were given a full physical assessment prior to taking part. Inclusion criteria included:

1. Complete spinal cord lesion between thoracic level 3–12 (T3–T12), of at least 1 year duration.

2. Age between 18-65 years.
3. No significant medical or psychiatric complications (assessed by clinician).
4. Sufficient range of motion at the joints (assessed by therapist).
5. No excessive spasticity (assessed by therapist).
6. Distal tibia and femur trabecular bone densities greater than 40 mg/cm^3 , measured by peripheral Quantitative Computed Tomography.
7. Ability to transfer safely between wheelchair and tricycle.
8. Willing to attend the clinic and to exercise at home according to the prescribed training programme.
9. Having space and the support at home to set up the tricycle ergometer for frequent use.

One subject (GLA) dropped out of the study after baseline testing due to an adverse autonomic response to stimulation and his data are therefore not included here.

Table 3.1: The Subjects

Subject	Gender	Age (yrs)	Lesion level	Years since injury	Height (cm)	Body mass (kg)
1	F	35	T7	15	162	64
2	M	43	T9	25	186	67
3	M	40	T4	11	184	70
4	F	45	T9	4	167	54
5	M	57	T4	9	173	85
6	M	44	T4	4	170	76
7	M	39	T3	8.5	177	83
8	M	38	T3	12	183	73
9	M	27	T6	3.5	173	59
10	M	48	T3	5.5	182	105
11	M	44	T9	20	175	74
Mean		41.8	5.5	10.7	175.6	73.6
SD		7.6	2.5	7	7.6	14

3.1.2 Muscle conditioning

To strengthen and increase the fatigue resistance of the leg muscles prior to cycle training, subjects completed a minimum of 6 weeks (14.2 ± 6.9 weeks (mean \pm SD)) of progressive, (up to 60 min per session with 1 kg ankle weights added as required and tolerated thereafter) dynamic, muscle conditioning at home on 5 days of the week.

Pairs of self adhesive surface electrodes¹ were placed proximally and distally to the motor point of the knee flexor and extensor muscle groups to be used during cycle training (detailed

¹PALS Platinum, Nidd Valley Medical Ltd.

in section 3.2.1. A Salisbury Odstock 4-channel stimulator (GLA) or an 8 channel Stanmore electronic stimulator² (LON and NOT) was used with a current controlled monophasic square wave stimulation pattern. Parameters were preset individually for each subject to optimise the muscle group contractions, using a pulse frequency of either 20 or 50 Hz and pulse duration of between 300 and 400 μ s. Intensity was controlled by altering the current amplitude between 80 and 150 mA. Stimulation was applied simultaneously to the flexors of one leg and the extensors of the other with a 1:1 duty cycle set at 6 seconds on/off, before stimulating the opposite muscle groups of each leg.

Subjects attended the laboratory for a cycling assessment after a minimum of 6 weeks of muscle conditioning to determine readiness for progression to cycle training. This was based on their ability to cycle continuously for at least 10 min with no external load applied. They were also required to be proficient in the use of the training equipment, in chair to tricycle transfer, and have enthusiasm and adequate support from those at home to be able to commence with the training programme. Progression to cycle training was determined on an individual basis and according to resource availability. Cycling equipment was then installed in the subjects homes and inspected regularly throughout the study.

3.2 Home training

3.2.1 Training equipment

Tricycle All training was performed at home on a commercially available mobile recumbent tricycle³ adapted for FES use. Fig. 3.1 shows some of the subjects preparing for an indoor sports event on their bikes. For home training, the tricycle was mounted on an electronically braked cycle trainer⁴ which supplied resistance to the rear wheel. Resistance at the pedals was also adjusted by manually changing the gearing.

Legs and feet were secured firmly to the pedals by rigid ankle orthoses to prevent movement around the ankle and constrain movement to the sagittal plane. Due to a combination of relatively short limb length and low bone density, one subject (NOT) used an adapted orthosis in conjunction with calf muscle stimulation. A throttle was attached to the left hand grip and interfaced with the stimulator software to allow the user to manually control stimulation intensity (as detailed in following paragraph). A shaft encoder mounted on the crankshaft relayed feedback of crank arm position to the stimulator software to permit angle specific muscle stimulation (see Table 3.2). Velocity compensation was incorporated in the stimulator software to respond to changes in angular velocity as the cadence varied during cycling. A hand held computerised interface was used to control the trainer resistance

²Salisbury, UK.

³Inspired Cycle Engineering Ltd., UK.

⁴Tacx Flow Ergotrainer, Wassenaar, Holland.



Figure 3.1: Some of the subjects preparing for an indoor sports day in Salisbury 2005. These tricycles were also used for home training purposes with the rear wheel mounted on an electronically braked cycle trainer. The stimulators can be seen attached to the frames of the tricycles in the foreground of the photograph.

and to display cycle cadence (pedal revolutions per minute).

Stimulator An 8-channel electronic stimulator⁵ was used with a monophasic square wave pattern to stimulate the quadriceps, hamstrings and glutei muscle groups of each leg via surface electrodes (detailed earlier). The *triceps surae* (calf) muscle groups were also stimulated in the 5 LON subjects as this group considered that this might augment knee flexion, and in one NOT subject as noted previously. The stimulator was programmed to deliver charge to each individual muscle group to achieve a smooth pedalling action. The current was individually predetermined (to achieve a palpable, smooth muscle contraction) within the range of 0–150 mA at a frequency of 50 Hz. Stimulation intensity was then controlled by adjusting the pulse duration, via the throttle, within the range of 0–510 μ s [86]. An typical example of the stimulation profiles used is shown in Table 3.2.

3.2.2 Cycle training protocol

Following completion of the muscle conditioning phase, subjects proceeded to the cycle training programme; for the first 8 weeks, subjects were required to train 3 times per week. This was increased to 4 times from week 9 to week 16 and then up to 5 times per week thereafter to an expected total of 236 sessions over 52 weeks. Individuals were also encouraged to include sessions of mobile cycling on level tarmac as part of their training programme. A

⁵Stanmore stimulator, Salisbury, UK.

Table 3.2: An example of muscle stimulation angles for one subject.

Stimulation angles	Muscle groups stimulated					
	Right			Left		
	Quadriceps	Hamstrings	Gluteals	Quadriceps	Hamstrings	Gluteals
Start Angles (degrees)	55	188	90	235	8	270
Stop Angles (degrees)	155	265	180	335	85	360

The computer-controlled, angle-specific and velocity compensated [86], pattern of stimulation for each muscle group was synchronised with respect to the crank position of the cycle or ergometer: 0° = the right crank arm centrally positioned at the top.

number of subjects on this study participated in the first FES sports day in September 2005 in Salisbury, and the first international FES sports festival in June 2006 in Cardiff.

During each session, stimulated cycling normally commenced after a period of one or two minutes of manually assisted, passive leg pedalling. This was to help minimise the occurrence of muscle spasms at the onset of stimulation. Stimulation was then applied fairly rapidly to SS point (over ~ 60 s) to enable the legs to turn the pedals.

Training started with no trainer resistance applied to the back wheel at a cadence of 50 rpm, pedalling for as long as possible up to 60 min, or until cadence dropped to about 30–35 rpm, when cyclists were then permitted to assist the stimulated legs using their hands to complete the session. When subjects were able to complete three 60-min sessions of unloaded, unassisted cycling, trainer resistance was applied to the back wheel from the start of the next session. Subjects were advised to revert to unloaded cycling should they experience feelings of nausea following the large step between unloaded cycling and the first resistance level. Resistance was then reintroduced after a suitable recovery period.

The electronically braked cycle trainer did not give an accurate measure of the training work rate in Watts (unlike the motorised cycle used in testing) during the HTS, nonetheless the trainer was always set to the highest resistance level that the subjects could pedal against at 50 rpm (HRL). Resistance was lowered or removed when cadence dropped to about 30–35 rpm to complete the session. Once subjects were able to complete 10 min of continuous pedalling against their HRL on 3 consecutive sessions (the subsequent 50 min of these sessions were completed at a reduced load or unloaded), the trainer resistance was increased by one increment at the start of the following session. The subjects were exposed to progressive resistance in subsequent training sessions in this manner to ensure that maximum training stimulus was always applied from the start of each session. If training was disrupted by holidays or illness, then subjects resumed training as soon as possible thereafter. If they subsequently found themselves unable to pedal against their last HRL, they resumed training at lower resistance until they regained their lost fitness.

3.3 Physiological testing

An IWRT to stimulation saturation (SS) point (100% of the min-max range) was performed in the week prior to commencing cycle training and then after 3, 6, 9 and 12 months, where peak values for outcome measures (detailed later) were estimated. A CWRT, set at 70% of the initial P_{peak}^t was then performed for up to 20 min at least 24 hours after the IWRT and after 3, 6, 9 and 12 months of training. The development and pilot testing of these protocols is fully described in [55]. A HTS was also monitored for 8 of the subjects after 12 months of training, where heart rate and gas exchange variables were recorded continuously.

All subjects were familiarised with each test at least one week prior to the baseline tests. Subjects reported for testing rested and in good health. They were instructed to refrain from strenuous exercise or alcohol consumption in the preceding 24 hours, and from consuming food or caffeine in the preceding 2 and 4 hours respectively.

3.3.1 Testing equipment

Laboratory Tricycle Subjects were tested in the laboratory on a motorised trike⁶ adapted for FES use (Fig. 3.2). It was fitted with a crankshaft mounted power sensor⁷ which was integrated with control software run on a laptop PC to allow accurate control of cycling cadence and quantification of total leg power output, including the internal work required to rotate the legs (P^t). Power output was feedback controlled via automatic adjustment of stimulation intensity (this system is fully described in [86]). The tricycle boom length was individually adjusted to permit a comfortable recumbent cycling motion and this was kept constant during training and from test to test.

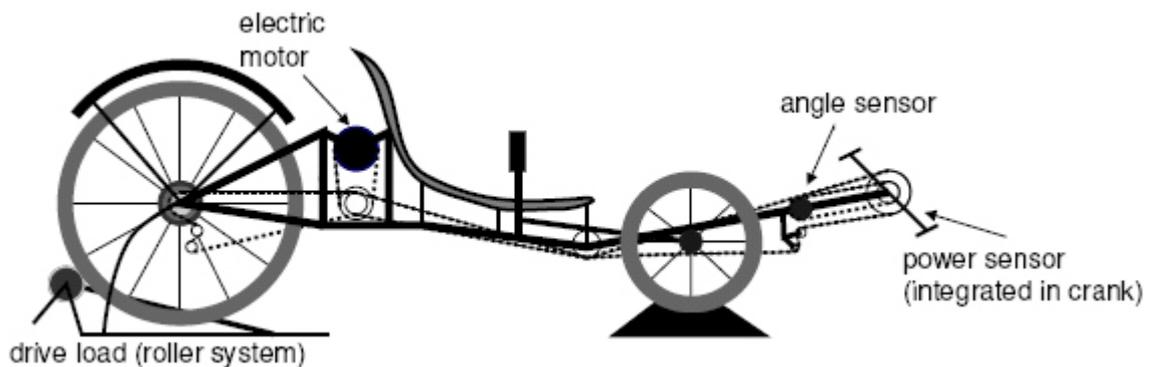


Figure 3.2: A schematic representation of the tricycle used for laboratory testing [85]

⁶Inspired Cycle Engineering Ltd., UK.

⁷SRM Powermeter, Schoberer Rad Messtechnik GmbH, Germany.

Metabolic cart Breath by breath and intra breath respiratory gas exchange measures were recorded using a low dead-space portable system in GLA and LON⁸ and a stationary system in NOT⁹. Prior to each test, the analyser was calibrated to a known volume and to certified calibration gas and ambient air according to the manufacturers instructions.

Blood lactate analysis systems Fingertip sample blood La^- enzymatic analysis was performed on samples taken during each test using a *Lactate II Champion* analyser¹⁰ (GLA) or a *Super GL easy* system¹¹ (LON). Earlobe samples were analysed using a *Super GL Ambulance* system¹² (NOT).

Pulse oximeter Heart rate (HR) and oxygen saturation were monitored continuously and recorded every minute using a fingertip sensor linked to a Datex-Ohmeda 3000 pulse oximeter system¹³.

Exercise perceptions ratings Ratings of perceived exertion (Borg 6–20 scale) and perceived breathlessness (Borg 0–10 scale) were assessed by presenting a card to the subject marked with the appropriate scale. The subject indicated their rating by pointing at the relevant number on the card.

3.3.2 Test protocol

Both the IWRT and the CWRT were conducted at a cadence of 50 rpm. A warm up of 7 min cycling at the lowest stimulated work rate (the lowest rate of stimulation that permitted the legs to turn the pedals) was followed by a rest period of a minimum of 10 min where respiratory gases were required to stabilise and the respiratory quotient (RQ) was required to be between 0.75 and 0.9. Rest was continued until these criteria were met. This was followed by a minimum of 4-min passive (non-stimulated) motor-controlled cycling where variables were required to stabilise as for the rest period.

Incremental work rate test

After the period of passive cycling, stimulation was applied to allow the power output to increase at a rate of 1 or 2 W/min until SS point (pulse duration $510\mu\text{s}$) was reached. The rate was chosen for each subject to allow the test to be completed within 8–12 min [22]. The test ended with a recovery period where stimulation was reduced to the lowest stimulated

⁸Metamax II, CORTEX Biophysik GmbH, Leipzig, Germany.

⁹Oxycon alpha, Jaeger, Hoechberg, Germany.

¹⁰Analog Instruments Ltd., UK, Hammersmith, London, W6 OBA.

¹¹Diasys Diagnostic systems, GmbH, Germany.

¹²Ruhrtaal Labor Technik, Mönnesee-Delecke, Germany.

¹³Datex-Ohmeda Inc., P.O. Box 7550, Madison, USA.

work rate for approximately 6 min to assist cardiac return and minimise the risk of peripheral venous pooling.

Constant work rate test

After the required minimum period of passive cycling, stimulation was applied to allow the power output to reach 70% of the IWRT P_{peak}^t . Stimulation was then adjusted continuously to allow the cycling power to be kept constant for 20 min or until the required power output could not be maintained. This was followed by a recovery period consisting of approximately 8 min passive cycling. This slightly extended recovery period was chosen for the passive recovery during this test since there was no active skeletal muscle pump to assist venous return.

Blood sampling and exercise perception ratings

Fingertip samples (GLA and LON) Arterialised blood samples were collected from the fingertip of a warm hand. This was warmed before the start of the test by immersing the hand in warm water ($\sim 40^\circ\text{C}$). The finger was then prepared by wiping with a sterile alcohol wipe¹⁴ before lancing with a disposable lancet. Approximately $15\mu\text{l}$ of blood was collected and stored in a capillary tube. Tubes were stored in ice for about 3 hours (analysis was conducted in a different location to the tests) and returned to room temperature prior to analysis.

Earlobe samples (NOT) The earlobe was prepared by wiping with a sterile alcohol wipe and then lanced with a disposable lancet. Blood samples were collected, stored and analysed according to the system manufacturer's instructions¹⁵.

Blood samples were taken at the following stages of the IWRT and the CWRT:

- Rest, prior to warm-up
- Rest, in the first minute post warm-up
- Rest, 1 min prior to onset of passive exercise
- Passive, 1 min prior to onset of first work load
- IWRT, in the first minute of exercise and every 3 minutes (15 seconds prior to work load increase) and then at SS point
- CWRT, after 10 min of exercise and then at 15 and end exercise
- Recovery, after 1, 3 and 5 minutes of recovery

¹⁴Professional Disposables International, Flint UK.

¹⁵*Super GL Ambulance* system, Ruhrtal Labor Technik, Möhnesee-Delecke, Germany.

Borg scale ratings of perceived exertion and breathlessness were noted 15 s prior to each blood sampling event for both tests.

3.4 Outcome measures and analysis

3.4.1 Outcome measures

Metabolic gas exchange The following variables were recorded continuously during each test:

Oxygen uptake (\dot{V}_{O_2})

Carbon dioxide production (\dot{V}_{CO_2})

End tidal oxygen pressure ($P_{ET}O_2$)

End tidal carbon dioxide pressure ($P_{ET}CO_2$)

Respiratory exchange ratio. ($\dot{V}_{CO_2}/\dot{V}_{O_2}$) (RER)

Minute ventilation (\dot{V}_E)

Tidal volume (V_T)

Breathing frequency (B_f)

Duration of inspired breath (t_i)

Duration of expired breath (t_e)

Fraction of oxygen in inspired air (F_iO_2)

Prior to analysis, the raw data were systematically edited to remove outlier data that were likely to have been caused by non-metabolic fluctuations in respiratory exchange [147]. Using a custom made graphical user interface programmed in Matlab (The MathWorks inc.), the raw breath by breath data were first re-sampled to provide at least 4 regular sample intervals between each breath. The evenly spaced data were then filtered by a non-phase-shifting low pass filter to give a second data set. This was then subtracted from the actual data values to give an error (residuals) data set, which was edited to remove any data points that lay beyond 3 standard deviations (a histogram of the residuals was generated to check that the normal Gaussian distribution had not been unduly truncated by the removal of this data). The edited raw data sets were then used in the subsequent data analysis.

The Peak (IWRT) or highest (CWRT and HTS) values were determined over a 60 second rolling average (the averaging window chosen reflects the relatively high data ‘noise’ observed

[147]) and steady state mean values for the rest and passive phases were taken as the average of the last 2 min of each stage. Exercise steady state values for the CWRT were the average of the last 5 min of this phase. Mean values during the HTS were taken over the last 57 min of exercise.

Cycling power output Power data were filtered with a non-phase-shifting low pass filter with a bandwidth of 25/60 Hz (half of the pedal cadence frequency) to ensure that any noise or disturbances occurring more regularly than this frequency were ignored.

During passive cycling (i.e. cycling with stimulation switched off) the legs were turned at a constant cadence by the motor alone, resulting in measurement of a negative work rate at the crankshaft . This corresponded to the rate of work required just to rotate the passive legs and was included in P^t [86]. P_{peak}^t was measured as the highest P^t value reached, which always occurred either before or at SS point.

Blood lactate sampling The La^- reagent, Lactate Oxidase was mixed with 5 μL of blood within the analyser. In the presence of molecular oxygen, La^- is oxidised by the enzyme Lactate Oxidase to pyruvate and hydrogen peroxide. Under the conditions of the assay, oxygen consumption is directly proportional to lactate concentration (GLA and LON). Samples were prepared and analysed according to the system manufacturer's instructions (NOT). Each sample was analysed at least twice. Values given are millimoles per litre (mmol/L).

Incremental work rate test

Peak values for all outcome variables were determined at SS point to allow valid test-to-test comparisons to be made, since tests ended at arbitrarily differing time points and often before \dot{V}_{O_2} had reached a plateau. Accordingly, the true peak values were not determined here. Outcome variables of interest during this test were: P_{peak}^t , $\dot{V}_{\text{O}_2\text{peak}}$, $\text{net}\dot{V}_{\text{O}_2\text{peak}}$ (the $\dot{V}_{\text{O}_2\text{peak}}$ of stimulated work only, calculated by subtracting mean passive exercise \dot{V}_{O_2} from $\dot{V}_{\text{O}_2\text{peak}}$), peak heart rate (HR_{peak}), peak oxygen pulse (O_2 pulse, calculated by dividing $\dot{V}_{\text{O}_2\text{peak}}$ by HR_{peak}) and the dynamic oxygen cost ($\Delta\dot{V}_{\text{O}_2}/\Delta P^t$), calculated as the slope of the linear fit of the \dot{V}_{O_2}/P^t relationship.

Constant work rate test

Mean values were taken as the average over the last 5 min of the exercise phase and were: P^t , \dot{V}_{O_2} , $\text{net}\dot{V}_{\text{O}_2}$ (the \dot{V}_{O_2} of stimulated work only, calculated by subtracting mean passive exercise \dot{V}_{O_2} from mean \dot{V}_{O_2}), $\dot{V}_{\text{E}}/\dot{V}_{\text{O}_2}$ (the ratio of \dot{V}_{E} to \dot{V}_{O_2}), RER^{16}), and La^- . The

¹⁶Due to the uncertainty regarding the degree of \dot{V}_{CO_2} produced as a consequence of anaerobic respiration, and tissue O_2 and CO_2 storage, the term RER was used here in preference to RQ, which is commonly used

highest RER_{high} was taken as the highest value of a 60 s rolling average at any time during the exercise phase.

The electrical cost of stimulation (stim/P^t) was calculated and is a development of the recently devised measure of the stimulation charge rate during FES cycling [84]. This was extended to relate the cost of stimulation to each W of P^t power produced and was determined by first calculating the charge applied to each muscle group per stimulation pulse: this was calculated as the product of the mean instantaneous pulse duration and current amplitude. Account was then taken of the on/off stimulation angles for each muscle group during each pedal rotation, and of the pedalling cadence (50 rpm). The mean values for each muscle group over the last 5 min were summed to give the total stimulation charge applied to the leg muscles per minute. The total charge was then expressed relative to P^t as $\mu\text{C}/\text{min}/\text{W}$.

Final home training session

Outcome variables of interest during the final HTSs were the mean values over the last 57 min of exercise, and the highest 60 s rolling average values for: \dot{V}_{O_2} , RER, $\dot{V}_{\text{E}}/\dot{V}_{\text{O}_2}$, and HR.

3.4.2 Statistical analysis

Using Minitab 13 software (Minitab Inc., USA), all data and model residuals were examined for normality of variance and distribution (Anderson-Darling test) prior to analysis to validate parametric testing methods. They were found not to be different from normal ($P > 0.05$). Due to the differences in individual response to training, and because the analysis was a time series analysis of non-independent data, within-subject modeling was used here in preference to a repeated measures analysis (other suitable methods include multivariate ANOVA, adjusted univariate ANOVA or mixed models) [81]. Paired t -tests (2-tailed) were performed between each consecutive test and between each test and baseline values. Bonferroni adjustments were not applied because the t -tests were not independent of each other [81]. Where differences reached significance ($P \leq 0.05$), the delta values were further analysed adopting a summary approach to preserve independence of data [68]. Multiple Pearson product-moment correlations were run between absolute and delta values and possible sources of variance. These included subject age, weight, height, years post-injury, lesion level and training duration. Regression analyses or general linear models (GLM) were then performed where associations were found to be significant. Differences are expressed in mean absolute terms with the standard deviation (mean SD) and the mean of all individual changes relative to baseline (mean %) where appropriate.

where exercise is primarily oxidative and the ratio is indicative of substrate use [173]

Chapter 4

Adaptations in peak responses after training

Learn from yesterday, live for today, hope for tomorrow. The important thing is not to stop questioning.

Albert Einstein

The effects of a 12-month, high-volume, FES cycle training programme on peak cardiorespiratory and power capacity in 11 individuals with paraplegia was examined in this chapter. These outcomes were presented at an international conference in July 2007 as detailed below and this work forms the basis of a paper that has been accepted for publication in September 2008 by the ACSM's peer reviewed journal, *Medicine & Science in Sports & Exercise*, also detailed below:

H.R. Berry, C. Perret, B.A. Saunders, T.H. Kakebeeke, N.De N. Donaldson, D.B. Allan and K.J. Hunt, "Cardiorespiratory and power adaptations to stimulated cycle training in paraplegia," *Medicine and Science in Sports and Exercise*, vol. 40, no. 9, 2008, in press.

H.R. Berry, K.J. Hunt, C. Perret, N. Donaldson, T.H. Kakebeeke and D.B. Allan, "Cardiorespiratory adaptations to 12 months of high volume functional electrically stimulated (FES) cycle training in paraplegic subjects." *46th International Spinal Cord Society Annual Scientific Meeting, Reykjavik, Iceland, 27 June to 1st July, 2007.*

4.1 Introduction

As discussed in chapter 1, people with spinal cord injury (SCI) often become very sedentary, which leads to low cardiorespiratory fitness levels and many of the many co-morbidities

associated with inactivity, including obesity, type 2 diabetes, and cardiovascular disease [126]. Physical activity has been found to have a preventative and therapeutic role for these conditions, with the greatest improvements in health being gained by the least fit when they become physically active. Thirty minutes of moderate daily activity, performed at a \dot{V}_{O_2} of around 1000–1500 mL/min for men or 700–1100 mL/min for women, is reported to be the minimum requirement for minimising health risks [170]. However, the $\dot{V}_{O_{2peak}}$ of untrained SCI wheelchair users rarely meets the minimum \dot{V}_{O_2} required to be sustained for this duration of activity (see section 1.2.2).

4.1.1 Electrically stimulated cycling

The relatively small muscle mass used during upper body exercise, the risk of shoulder pain from overuse [24], and the deleterious effects of possible injury on ADLs have led to the research and development of FES lower limb exercise systems [75, 86, 134, 137]. These systems allow temporary restoration of function to the paralysed lower limb muscles where stationary or mobile exercise training can then be performed.

4.1.2 FES cycle training programmes

In addition to the many diverse physiological benefits reported to have been gained by complete lesion SCI subjects after periods of FES cycling, significant, but variable, improvements in $\dot{V}_{O_{2peak}}$, peak power output (P_{peak}^t) and endurance have also been reported. Studies to date have investigated the responses of individuals with SCI during clinic-based FES cycle training studies of between 6 weeks and 12 months duration. Training regimes have varied in work rate (0–42 W), duration (5–60 min), frequency (two to three times per week), and test protocol (continuous or discontinuous), with some studies including a preparatory muscle conditioning period before or after baseline testing (see section 2.4).

4.1.3 Peak power and cardiorespiratory tests

A lack of consistency in methodology, test protocol, data treatment and analysis across studies was identified in chapter 2. This has made the direct comparison of results across studies difficult if not invalid. Additionally, the relatively large power increments (~ 6 W) used in all previous tests resulted in a lack of measurement sensitivity and ability to detect small but perhaps clinically important changes in power and $\dot{V}_{O_{2peak}}$ over time.

4.1.4 Study aims and objectives

As an advance on the pedalling drive torque measurement test bed developed by Gföhler *et al.* [61], a recently developed integrated feedback system was used for exercise testing that allowed simultaneous feedback control of power via automatic adjustment of stimulation and

electrical motor control of cadence. This permitted the application of arbitrarily small work rate increments and accurate quantification of power output even during unloaded cycling [55, 86]. Unlike other FES training studies, the home-based training programme followed in the present study allowed individuals to optimise their time management and maximise their training within the prescribed high volume limits. The relationships between the training hours completed for each subject, and the magnitude of change in peak cycling power (P_{peak}^t) and $\dot{V}_{\text{O}_2\text{peak}}$ that they achieved were able to be examined.

The aim of this part of the study was therefore to investigate the power and the cardiorespiratory adaptations to a progressive, high-volume, home-based 12-month FES cycle training programme using a novel, sensitive test bed. This permitted high resolution, systematic and consistent power and respiratory gas exchange analyses to be performed for the first time in FES cycling. From this a training dose-response analysis was performed, and the feasibility and the viability of home-based FES cycle training for improving and maintaining cardiorespiratory fitness by individuals with paraplegia was examined.

4.2 Methods

Please refer to chapter 3 for a full and detailed description of the methods and of the statistical analysis employed here.

Subjects The data for all 11 subjects that completed the training study were used for this analysis. Subject details are given in Table 3.1 on page 38.

Tests An IWRT was performed before and after 3, 6, 9 and 12 months of FES cycle training.

Outcome variables Outcome variables of interest during this study were: P_{peak}^t , $\dot{V}_{\text{O}_2\text{peak}}$, $\text{net}\dot{V}_{\text{O}_2\text{peak}}$, HR_{peak} , O_2 pulse.

4.3 Results

4.3.1 Training

Total training hours completed were 189 ± 36 h, which comprised a total of 197 ± 34 training sessions of 57.6 ± 5.0 min, 3.7 ± 0.6 times per week for 53.3 ± 3.9 wk over a period of 57.3 ± 6.2 wk. Training frequency compliance (s/w) was at its highest at 91% during the first 3 months of training and declined to 85%, 78%, and 75% during the last three quarterly training periods. Total training duration compliance (h completed) for each training period was 85%, 95%, 78%, and 78% (the target and mean recorded values for training frequency and duration are given in Fig. 4.1). Continuous cycling capacity increased from 10–60 min of pedalling over the course of the study for all subjects.

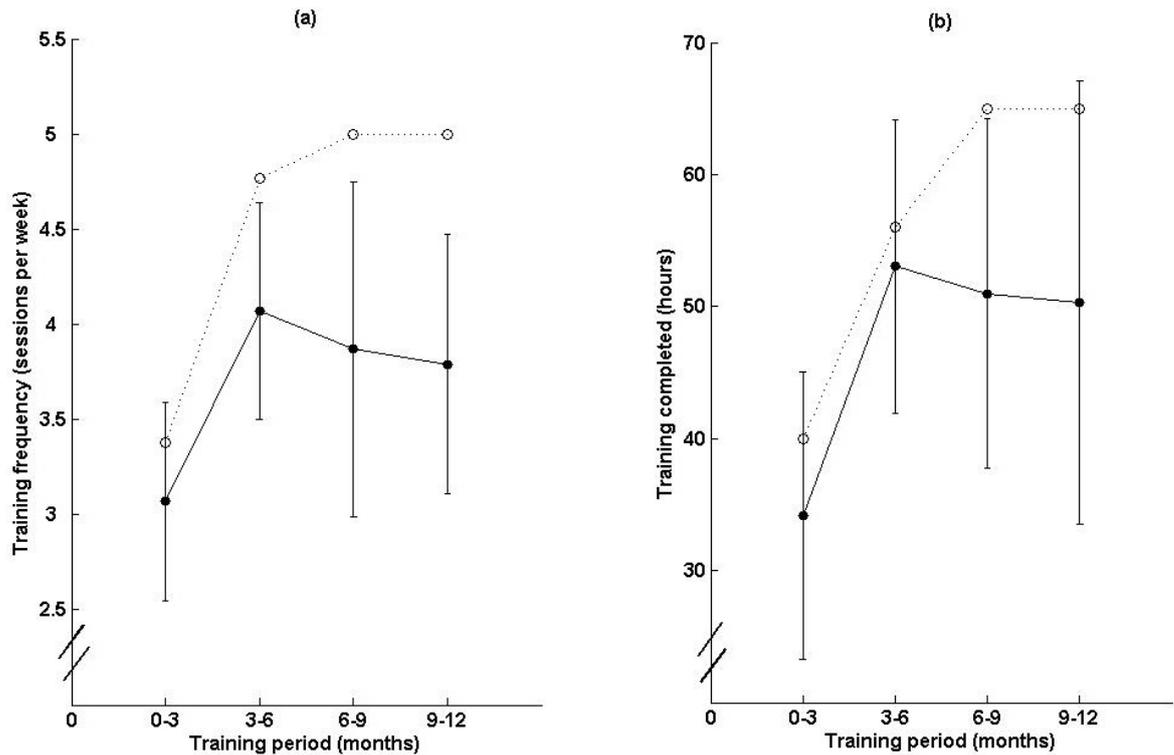


Figure 4.1: Training frequency (s/w) and (a) the total number of hours completed during each training period (b). The open circles represent the target values for each period, and filled circles are the mean recorded values, with the error bars indicating the SD.

4.3.2 Peak power output

Outcomes are summarised in table 4.1 and given in Fig. 4.3. A graphic representation of the power response to stimulation is given in Fig. 4.2. P_{peak}^t was measured as the highest filtered power value reached which occurred either before or at SS point, after which time power often dropped in level (Fig. 4.2). The greatest increase in P_{peak}^t occurred within the first 3 months of training ($P = 0.02$) with a further increase measured between 3 and 6 months ($P = 0.009$; Fig. 4.3(a)). Changes after this time were not significant, resulting in a significant mean relative increase of 132% ($P = 0.001$) after 12 months. Individual responses ranged from a loss of power of 0.7 W to an increase of 25.8 W with final values ranging from 6.7 to 35.6 W (for mean values, see Table 4.1).

The increases in P_{peak}^t between 0 and 6 months of between 0.77 and 20.82 W were significantly related to total training hours completed during this time, which ranged from 59 to 114 hours. This relationship ($r^2 = 0.84, P < 0.001$; Fig. 4.4(a)) was not found thereafter ($r^2 = 0.03, P = 0.60$). Additional calf muscle stimulation did not affect P_{peak}^t differences between tests or overall ($P = 0.36$). Variance in pre training P_{peak}^t was explained by sex ($P = 0.043$), where female values were lower, but this did not account for any of the variance in the magnitude of change ($P = 0.46$) or absolute values after training ($P = 0.14$).

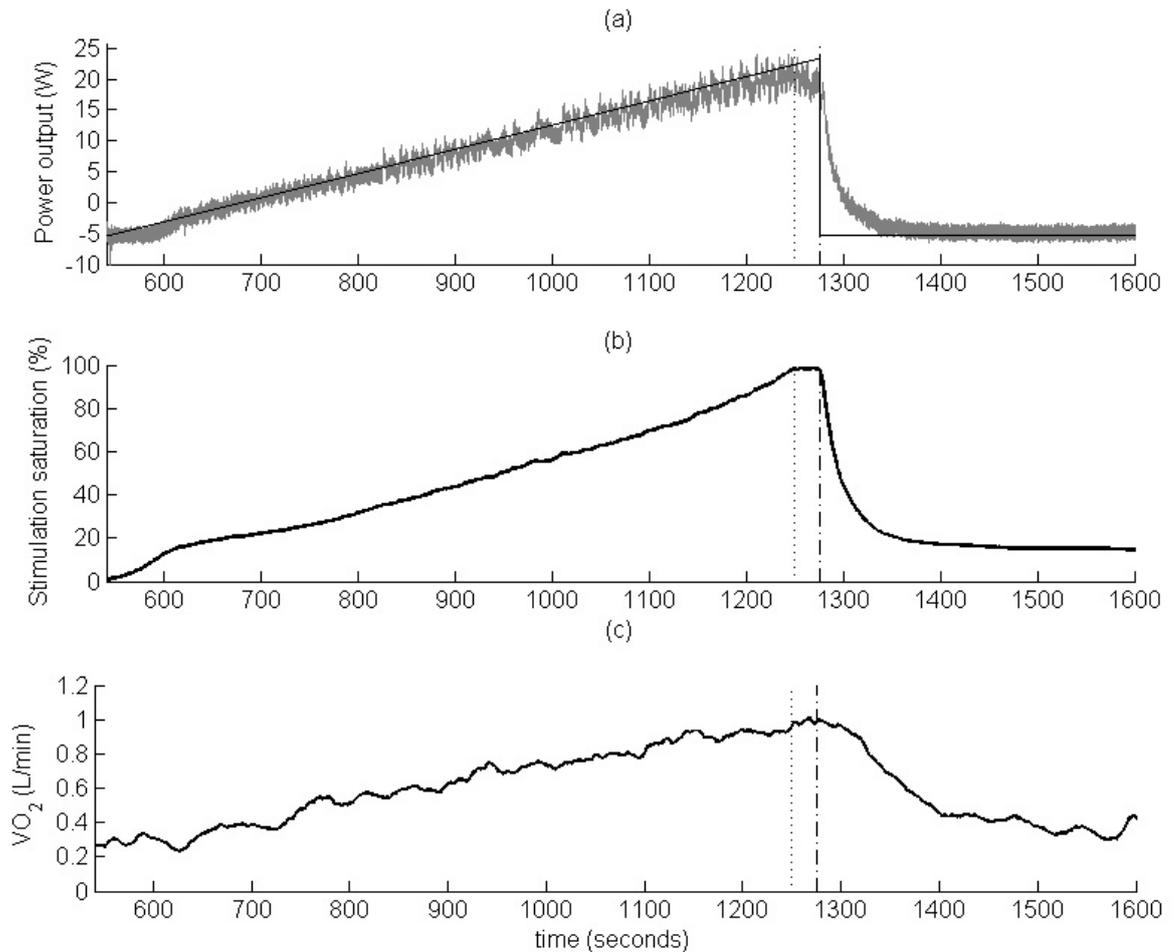


Figure 4.2: The power and $\dot{V}O_2$ response for one subject from the application of stimulation to SS point (100% of stimulation min-max range) and during recovery. Vertical dotted lines indicate SS point and vertical dashed line indicates the time at which stimulation was reduced to the lowest stimulated work rate. Panel (a) shows the reference power (black line) and the actual power response to stimulation (grey). Note the slight dip in power just after SS point was reached. Panel (b) shows the stimulation pulse-duration as a percentage of its min-max range. Panel (c) shows the $\dot{V}O_2$ response to the incrementing load (a 9-breath average is used here for clarity.)

4.3.3 Cardiorespiratory adaptations

All significant change in $\dot{V}O_{2\text{peak}}$ occurred between 3 and 6 months ($P = 0.003$). However, when expressed net of passive $\dot{V}O_2$, net $\dot{V}O_{2\text{peak}}$ had significantly increased between 0 and 3 months ($P = 0.023$; Fig. 4.3(c)) with a mean relative increase of 168% overall ($P < 0.001$; for mean values, see Table 4.1). The changes over the first 6 months were significantly related to total training hours completed ($r^2 = 0.52$, $P = 0.012$; Fig. 4.4(b)). The relationship revealed that between ~ 80 and 90 h or ~ 3 to 3.5 h of training per week were required to have been completed over this time to achieve an improvement in $\dot{V}O_{2\text{peak}}$ of 1 MET.

HR_{peak} (Fig. 4.3(c)) increased by 13% after 6 months ($P = 0.008$), but by 12 months the increase just failed to reach significance ($P = 0.057$; Table 4.1). Peak $O_2\text{pulse}$ had increased

Table 4.1: Summary of incremental work-rate test outcomes.

Outcome variables	0 months	3 months	6 months	9 months	12 months
$\dot{V}_{O_2\text{peak}}$, mL/min	543±148	651±271	**††819±267	††802±277	††820±226
net $\dot{V}_{O_2\text{peak}}$, mL/min	247±125	†374±240	**††510±241	††530±243	††524±217
P_{peak}^t , W	8.5±3.3	†13.5±7.6	**††17.8±8.5	††18.7±7.6	†18.2±8.8
HR _{peak} , bpm	82.3±8.1	†88.2±12	*†90.9±13.2	††93.6±13	92±16.3
O ₂ pulse, mL/beat	6.70±1.65	†7.17±2.15	*††8.80±1.95	†8.47±2.37	††9.37±1.11

Data are means \pm SD. Peak values were taken at SS point (100% of stimulation min-max range). $\dot{V}_{O_2\text{peak}}$ peak oxygen uptake, net $\dot{V}_{O_2\text{peak}}$ peak oxygen uptake net of passive, P_{peak}^t peak power, HR_{peak} peak heart rate, O₂ pulse pulse oxygen uptake per heart beat, Paired *t*-tests were performed between each consecutive test and between each test and baseline. * Significantly different from preceding test-point, or † from baseline at $P < 0.05$, ** Significantly different from preceding test or †† from baseline at $P < 0.005$.

($P = 0.002$) by 6 months, with no significant change thereafter ($P = 0.85$; Fig. 4.3(d)), leading to a mean relative increase of 35% after 12 months ($P = 0.002$; Table 4.1).

None of the variance in any of the outcome variables was significantly explained by stimulation protocol, years post-injury, lesion level, or age.

4.4 Discussion

The aim of this study was to examine the extent to which progressive, high-volume, home-based FES cycle training could improve $\dot{V}_{O_2\text{peak}}$ and cycling power in paraplegic individuals. Due to substantial muscle disuse atrophy after SCI, internal work may represent a relatively large proportion of total work done, and in some cases subjects may not even be capable of sufficient internal work to overcome frictional losses and to move the legs [85]. This is the first longitudinal study to measure and account for this work when quantifying total power output during FES cycling tests. Furthermore, work rate was able to be increased by arbitrarily small increments (here, 1 or 2 W) during the IWRTs unlike the $\frac{1}{8}$ kp or approximately 6.1 W increments (assuming a cadence of 50 rpm) used during all previous FES cycling studies. This permitted a sensitive training dose-response analysis to be made for the first time in ES exercise. This type of protocol is also particularly important for examining cardiorespiratory responses such as gas exchange thresholds that require analysis with a high temporal resolution. Although the absolute magnitude of any change in power of less than 6.1 W is small, the relative change for these individuals is substantial and may reflect clinically significant adaptations.

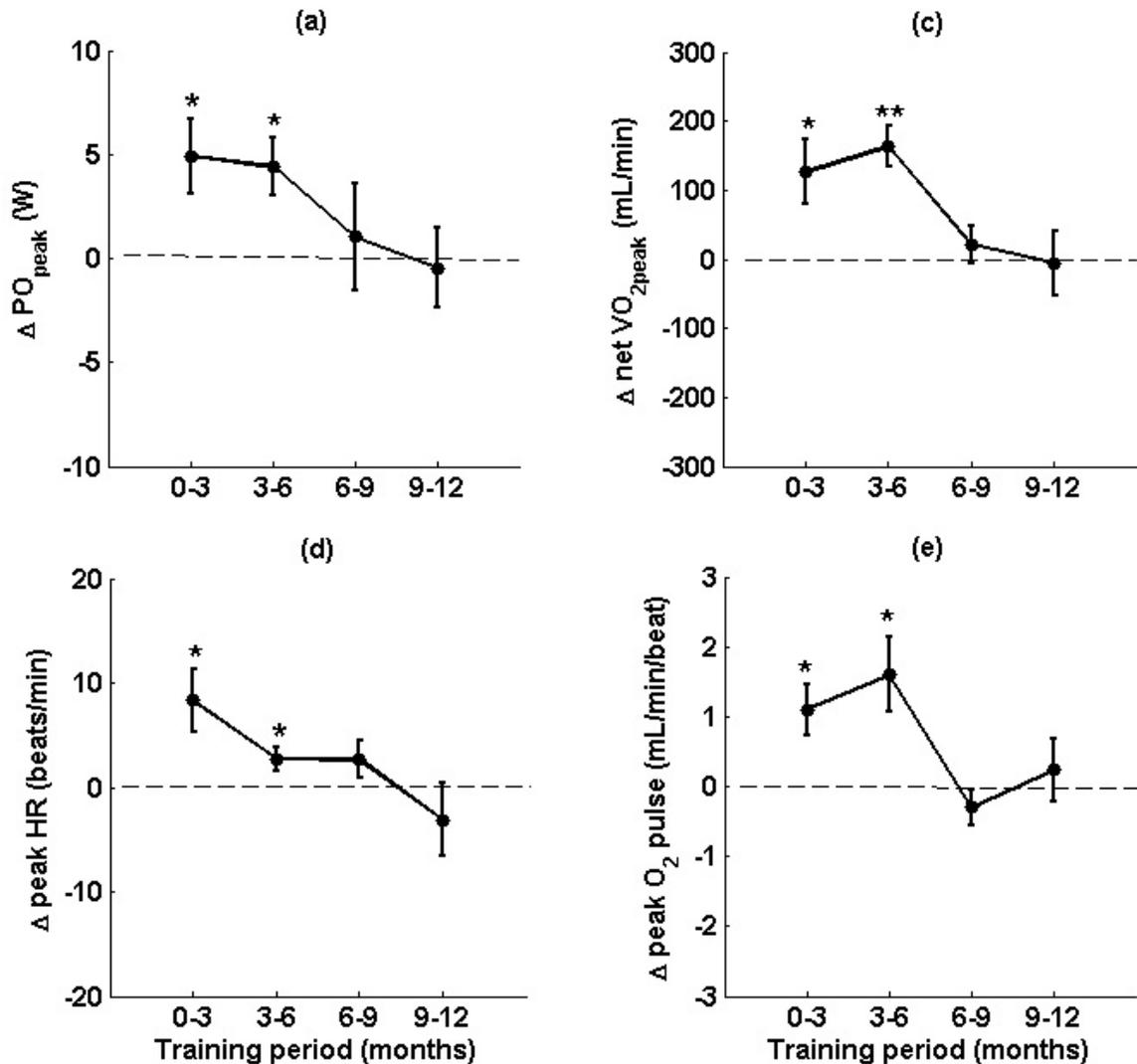


Figure 4.3: IWRT results showing the delta (Δ) values between each consecutive test for (a) P_{peak}^t , (b) net $\dot{V}_{\text{O}_2\text{peak}}$, (c) peak HR, and peak O_2 pulse. The horizontal dashed line represents no change. Data are presented as mean \pm SEM (shown here in preference to SD to account for the n compared during each test point). Peak values were taken at SS point (100% of stimulation min-max range). Two-tailed paired t -tests were performed between each consecutive test. *Significantly different where $P \leq 0.05$; **significantly different where $P \leq 0.001$.

4.4.1 Peak power output

The highest individual P_{peak}^t value of 35.6 W (internal plus external work rate) achieved in this study after 12 months of training is similar to that measured by the same technique in a case study subject with tetraplegia after a similar training programme [95]. Nonetheless, there appear to have been no greater gains in power by training more frequently for longer durations than that in previous studies: The P_{peak}^t value here is also similar to the highest work rate (external work measured only) achieved by Ragnarsson *et al.* [144] during training after only 36 sessions over 12 wk. They found that their subjects ($N = 19$) could cycle within

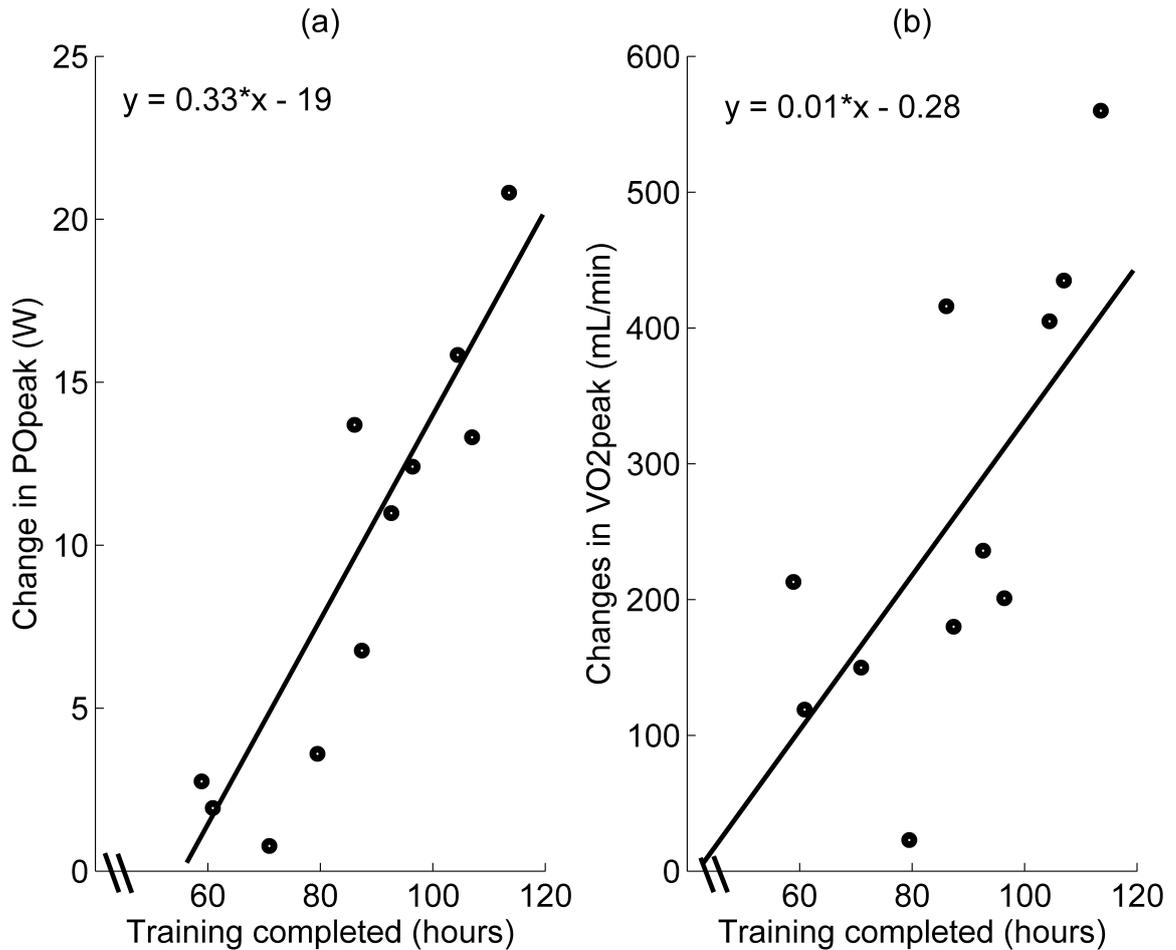


Figure 4.4: Regression plots showing the relationship between total training duration and changes in (a) P_{peak}^t between 0 and 6 months where $r^2 = 0.84$, $P < 0.001$; and (b) changes in net $\dot{V}_{\text{O}_2\text{peak}}$ between 0 and 6 months where $r^2 = 0.52$, $P = 0.012$. The equations for each regression line are shown on each plot. Data are for 11 subjects.

a range of 0 to 36 W for 15 min, most of whom ($n = 17$) cycled at between 0 and 12 W. After only twenty-four 30-min sessions of exercise (~ 8 wk) Barstow *et al.* [11] reported a mean PO_{peak} of 14.5 ± 5.6 W similar to the P_{peak}^t value of 13.5 ± 10.7 W found in this study after thirty-nine 60-min sessions (~ 12 wk).

Test protocol Studies have used either continuous [11] or discontinuous [56] test protocols using 5-min work rate increments of ~ 6 W ($\frac{1}{8}$ kp at 50 rpm) to peak exercise tolerance. The protocol adopted by Figoni *et al.* [56] interspersed four 5-min bouts of FES cycling with 4 min of passive exercise and rest. In addition to having many complete lesion subjects, their protocol, in contrast to that used by Barstow *et al.* [11] and by this study, may have allowed for sufficient muscle recovery during the rest and the passive exercise intervals to account for the relatively high power output values recorded by their untrained subjects (15 ± 7

W). The methods or the calculations used for determining PO_{peak} are not detailed in these studies, where it is not clear whether PO_{peak} values were estimated by linear extrapolation between the 6-W increments during the final 5-min increment or given as the final work rate tolerated. The combination of differences in subject group, test protocol, and PO_{peak} calculation methods makes direct comparisons between studies difficult, if not invalid.

Motor unit recruitment There are two substantial differences between voluntary activation in able-bodied subjects and transcutaneous electrical stimulation of persons with SCI. First, the axons are recruited in a disorderly way [69], neither orderly according to the Henneman size principle (small to large) nor the reverse as if the electrodes were close to the nerve trunk. Second, most muscle fibres become FG [139], and although some may convert towards slower phenotypes as a result of the training, the pre-injury relationship between axon diameter and muscle type will not be restored. We should therefore expect that as the stimulation intensity increases towards SS point, more and more muscle fibres will be recruited but the proportion of the types will remain constant (and probably predominantly FG). The combination of stimulation application rate and muscle fibre fatigue rate will determine the momentary cross-sectional area of recruited muscle mass available for power production; during cycle training, the rapid stimulation application rates (~ 60 s to SS) and the initial HRL would result in a relatively high short-term anaerobic power output followed by fatigue to a sustainable power output. This would reflect the mean balance between fibre fatigue and recovery rates and the muscles oxidative capacity, notwithstanding the effects on power of possible antagonist co-contraction or muscle spasms. The power profile would be similar to that observed during volitional all-out cycling [166], and indeed this has been observed by Theisen *et al.* [161], except that they found power to recover slightly after the initial drop from the highest power output.

Point of measurement During the IWRT, however, stimulation and load application rates were progressive over 8 to 12 min, by which time a degree of muscle fatigue is likely to have already occurred. Power values at this time are then likely to be lower than those that could be produced at the start of a training session when muscles are fresh and stimulation application rate is rapid. This could also explain some of the differences in PO_{peak} values measured across studies where load and stimulation application rate have either varied between subjects [119] or not been detailed, and the time of PO_{peak} measurement has not been given. Therefore, for future studies, the test protocol and the manner and time at which PO_{peak} is measured should be clearly stated to clarify which type of power is being measured, that is, peak explosive power, peak IWRT power, or endurance power.

Loss of P_{peak}^t The overall loss in power of 7% for one individual was explained by an examination of his training diary: after a successful training period between 3 and 6 months

where he recorded an increase in P_{peak}^t , his training became erratic and he took a 5 wk holiday in the 6 wk before his 9 month test and then completed only 27 of the expected 65 final training sessions. Discounting possible measurement error, this degree of reversibility in training adaptations is nonetheless quite remarkable.

4.4.2 Peak cardiorespiratory responses

Oxygen uptake The $\dot{V}_{\text{O}_2\text{peak}}$ tests provide an indication of the maximal oxidative capacity of the stimulated muscle mass, not of maximum systemic $\dot{V}_{\text{O}_2\text{max}}$ (see section 2.3), but provide a valuable insight into the metabolic stress that can be achieved by FES cycling alone nonetheless.

The mean improvement in IWRT $\dot{V}_{\text{O}_2\text{peak}}$ equated to just over 1 MET. Considering that an increase in $\dot{V}_{\text{O}_2\text{peak}}$ of only 1 MET is associated with a mortality benefit of about 20% [170], then it would appear that it is possible for 3 to 3.5 hours each week of FES cycling alone to be sufficient to reduce the health risks associated with inactivity and promote health benefits, especially because cycling sessions were sustained for twice as long as the recommended duration for this MET intensity of work [170, 73]. This is particularly important for previously sedentary individuals as they become active, but the plateau reached in $\dot{V}_{\text{O}_2\text{peak}}$ values (which are substantially lower than those that can be expected after similar periods of volitional cycling or running) illustrates the serious limitations of this type of exercise for further improvements in aerobic capacity for this subject group.

Data treatment The highest $\dot{V}_{\text{O}_2\text{peak}}$ value of 1.17 L/min found here is not dissimilar to those previously reported after training regimes of much lower frequencies and durations. The comparatively low $\dot{V}_{\text{O}_2\text{peak}}$ values attained in this study may be explained by the differences in data treatment and analysis found across studies rather than to a poorer exercise response; Mohr *et al.* [119] reported a mean $\dot{V}_{\text{O}_2\text{peak}}$ of 1.43 ± 0.09 L/min for 10 subjects and a highest individual value of 1.48 L/min, but it appears that, unlike this study, the breath by breath data were neither edited nor averaged before analysis, with peak values given as the highest absolute values within a 2 min period. This could lead to erroneously high estimates of peak values, distorted by outlier values, specially where the noise to signal ratio is high [147]. The mean sustainable \dot{V}_{O_2} during training may provide another, more meaningful, indicator of aerobic capacity for this subject group and for this type of exercise. This is examined and discussed in full in chapter 7.

Endurance capacity The increase in cycling endurance capacity from 10 to 60 min reflects improvements in muscle fatigue resistance and in oxidative capacity, with muscle fibres likely to have transformed from FG towards FOG isoforms [139]. Further investigations, including histological examinations of changes in muscle mass and phenotype, are needed in an attempt

to understand the underlying physiological adaptations to this unique exercise modality.

Heart rate Although HR_{peak} increased by 13% after 6 months, it was not significantly different from pre training levels by the end of the training programme and the post-training HR_{peak} of 92 ± 16 bpm equated to only 53% of the mean age predicted maximum, suggesting that exercise limitations are more likely to be peripheral rather than central in nature: parasympathetic innervation of the heart is unaffected by thoracic level SCI and so the normal reduction in outflow that occurs during exercise would enable the HR to increase to 100 bpm, even in the presence of a compromised sympathetic outflow (see Fig. 1.3 on page 5) [176].

Oxygen pulse The overall 35% increase in O_2 pulse indicates improvements in tissue O_2 extraction or to an increase in stroke volume (SV) or to both. Increased SV, which provides a more beneficial myocardial stress than an increase in HR, occurs during ES leg exercise due to the activation of the venous muscle pump [56] and has been found to be greater after FES leg cycle training than after arm cycle training [125]. The mean post-training O_2 pulse value was similar to the value observed by Barstow *et al.* [11] after only 24 exercise sessions, but again, direct comparisons are difficult because \dot{V}_{O_2} data treatment was not detailed.

4.4.3 Training dose-response

This is the first study to report a significant and robust relationship between the magnitude of change in P_{peak}^t and $\dot{V}_{O_{2\text{peak}}}$, and the total duration of training, however, this relationship was found only during the first 6 months of training. During this time, when training resistance and volume were both progressive, the greatest training duration of 114 h saw the greatest improvements in P_{peak}^t of 20.8 W and in $\dot{V}_{O_{2\text{peak}}}$ of 555 mL/min. Kakebeeke *et al.* [95] and Mohr *et al.* [119] also observed that significant increases in power and $\dot{V}_{O_{2\text{peak}}}$ occurred only within the first 6 months of training. In the present study, although training was always performed against the a maximally tolerated trainer load, training diaries revealed this was not able to be increased after about 6 to 9 months of training. This limitation could be physiological in nature or perhaps due to the training protocol or the stimulation strategies used and merits further investigation.

4.4.4 Feasibility of high-volume training

This is the first FES cycling study where subjects were required to train for 60 min per session for up to five s/w for 52 wk. Similar to the findings of an earlier case study where a subject with tetraplegia followed a similar training programme [95], training frequency and duration reached a peak between 3 and 6 months and then declined slightly thereafter. It appears that this high frequency duration and therefore overall volume of training, higher than any other

FES study to date, was neither feasible nor sustainable in the long term. The time taken to prepare for and complete each training session (~ 2 h) represents a substantial weekly time commitment, especially for those working full time or those with family responsibilities, and requires a great deal of motivation and family support to complete. The training plateau reached by 6–9 months may have affected motivation levels.

4.5 Conclusion

The current training resulted in significant, training volume-dependent cardiorespiratory and cycling power output adaptations during the first 6 months of training when training frequency, duration, and load were progressive. The upper limits in load tolerance were met during this programme, and it is not known whether this is due to a physiological limitation or to limitations in the stimulation strategy and the training protocol used. Further study is merited to develop and to evaluate different stimulation, loading and training strategies specific to ES exercise to optimise favourable training responses with lower training volumes for this subject group.

Chapter 5

The energetics of FES cycling: adaptations to training

The most exciting phrase to hear in science, the one that heralds new discoveries, is not Eureka! (I found it!) but rather, “hmm . . . that’s funny . . .”

Isaac Asimov

The metabolic and the electrical costs of stimulated work were estimated during FES cycling and the effects of training on these parameters are given and discussed in this chapter. The results from the preliminary study have been published in the *European Journal of Applied Physiology* and the work in this chapter is currently in preparation for submission as a journal article:

K.J. Hunt, B.A. Saunders, C. Perret, H. Berry, D.B. Allan, N. Donaldson and T.H. Kakebeeke, “Energetics of paraplegic cycling: a new theoretical framework and efficiency characterisation for untrained subjects”. *European Journal of Applied Physiology*, vol. 101, pp.277–285, 2007.

H.R. Berry, T.H. Kakebeeke, N. Donaldson, D.B. Allan and K.J. Hunt. Energetics of paraplegic cycling: adaptations to 12 months of high volume training. *European Journal of Applied Physiology*, in preparation.

5.1 Introduction

It is clear from the previous chapter that FES cycling can induce significant and important gains in $\dot{V}_{O_2\text{peak}}$, even where absolute cycling power is extremely low. This is due to the relatively high metabolic cost of FES cycling: where the purpose of FES cycling is to improve \dot{V}_{O_2} capacity, then this low work efficiency is advantageous, especially where initial power output is low. However, where mobility and recreation are the objectives, a higher level of work efficiency would be desirable.

5.1.1 FES cycling efficiency in untrained subjects

The efficiency of FES cycling was estimated and quantified during a preliminary study which investigated the energetics of 10 untrained individuals with paraplegia during constant work rate FES cycling. For this, a new extended theoretical framework was developed and specifically tailored to impaired subject groups with very little muscular power [85]. The new framework enabled a quantification of total work efficiency in the SCI individuals, based on calculations of the total internal and external work associated with turning the pedals at a constant motorised cadence, against an external resistance [86].

Despite the very low power output of only 6.2 ± 2.9 W (mean \pm SD) that was sustained over 10–20 min, the efficiency of FES work was able to be calculated. The O_2 cost of 38.8 ± 13.9 mL/min/W corresponded to an estimated total work efficiency of $7.6 \pm 2.1\%$, which is approximately one third of that expected during volitional cycling [85].

5.1.2 Sources of inefficiency

Estimates of the efficiency of ‘useful’ internal and external mechanical work will be influenced by the degree of extraneous ‘non-useful’ metabolic and muscular work also being done. This will depend on morphological, ergonomic, biomechanical and psychogenic factors including body frame size and mass, external drag factors, limb muscle and tendon architecture, skin surface to body volume ratio, external and internal mechanical effectiveness, metabolic coupling [30], skill and technique, and perceived exertion and cognition [122]. Internal mechanical effectiveness is dependent on the degree of muscle-tendon elastic energy storage and re-use, and metabolic coupling is influenced by genetic, physiological and biochemical factors such as muscle fibre type, the hormonal milieu and the efficiency with which ATP hydrolysis is coupled to muscular contraction [30, 35, 118].

5.1.3 Modifiable factors

Non-useful, extraneous work can be minimised in many ways: training and practice can improve technique and motor skills, and external mechanical effectiveness, or the relationship between the applied ‘used’ and ‘wasted’ forces, can be improved by reducing overall frictional losses, for example by reducing drag in swimming and running or changing the pedal trajectory or transmission systems in cycling [30, 112]. These adaptations and alterations can improve total work efficiency by increasing the proportion of the total \dot{V}_{O_2} that is used for useful, measured work.

5.1.4 Training and efficiency

Endurance and strength training can modify muscle-tendon architecture and alter body composition [152, 107] but it is unclear as to whether endurance training can improve work

efficiency. Cross sectional studies that have examined the effect of endurance training status on work efficiency have been equivocal, showing training to have opposing or no effects. There is some evidence that type I muscle fibres exhibit higher efficiency than type II [35], but other studies suggest that efficiency is unrelated to fibre type [87]. Yet others have found efficiency to be cadence-dependent for both fibre types [54, 108]. The higher efficiencies found in some endurance trained subjects may possibly be due to their higher percentage of type I fibres [118] or to improved substrate usage [160]. Longitudinal studies involving short term volitional cycle endurance training (6 weeks) have also found conflicting results [44, 77].

It is unknown whether long-term, high-volume FES cycle training can induce fibre type adaptations that are sufficient to increase the efficiency of this type of work. Observation of the changes in the anaerobic metabolite La^- and in the $\dot{V}_E/\dot{V}_{\text{O}_2}$ and RER over time, measured at the same absolute work rate, may provide valuable insights into any biochemical or physiological change in muscle that may affect the metabolic cost of work.

5.1.5 Sources of FES inefficiency

The very low work efficiency of untrained paraplegic cyclists is similar to that measured in anaesthetised able-bodied cyclists performing FES cycling [98]. This would suggest that the chronic effect of SCI, such as muscle atrophy, fibre type transformation towards a FG phenotype and reduced vascularisation are not particularly important factors in determining efficiency. The poor efficiency of FES cycling must then be attributable to the acute affects relating to muscle recruitment, stimulation timing and muscle activation patterns: muscle groups are not recruited in a physiological manner, but are recruited in a synchronous and non-selective manner [69]. Due to the stimulation paradigm, there is also a likelihood of antagonistic muscle group recruitment during ES exercise, particularly at high stimulation intensities. Additionally, the timing of muscle group activation is not usually adapted to cadence and power level, which it should be for maximum mechanical effectiveness.

Indeed, in a recent study that investigated the power-cost relationship between two different muscle activation patterns in one subject performing FES cycling, the metabolic and electrical cost of power production was found to differ for each activation pattern [84]. Although definitive conclusions cannot be drawn from data obtained from only one SCI subject, this lends support to the idea that the stimulation paradigm itself is a limiting factor in FES cycling efficiency.

The electrical (stimulation) cost of FES cycling has not yet been investigated between subjects or over time in any FES cycling study to date. The electrical cost of power production may give important insights into motor unit adaptations that may occur as a result of training. This cost is likely to be governed by the factors that determine motor unit recruitment, such as tissue impedance, nerve axon geometry and location within the muscle (see section 1.3.2) and by muscle contraction rate (pedalling cadence) [18]. Muscle and tendon architecture,

and the cross sectional area (CSA) of muscle mass within each motor unit will determine the power output capacity of each stimulated motor unit, and this may alter with a training induced fibre hypertrophy [94]. It is not known whether a period of progressive, high-volume FES cycle training can elicit such physiological adaptations within the motor unit that could potentially alter the electrical cost of stimulated exercise.

The aim of this study was therefore to investigate the effects of FES training on total work efficiency and on metabolic markers of anaerobic metabolism such as blood La^- concentrations and the RER. Efficiency was calculated within the newly developed energetics framework that accounts for both the useful internal and external work associated with turning the pedals. The relative electrical cost of stimulated work was also investigated for the first time during FES cycling by calculating the total electrical cost of muscle stimulation per Watt of total power produced (stim/P^t) and investigating the effects of regular training thereon.

5.2 Methods

Please refer to chapter 3 for a full and detailed description of the methods and of the statistical analysis employed here. Methods peculiar to this part of the study are given below.

5.2.1 Subjects

All 11 subjects that completed the 12-month cycle training programme were included in this study. Their details are given in Table 3.1 on page 38. For various technical reasons, full data sets were not available for all subjects at each test point. The number (N) of data points in each set is indicated in Table 5.1.

5.2.2 Exercise testing

A 20 min CWRT was performed prior to commencing the FES cycle training programme and after 6 and 12 months of training. The software controller was set to produce a cycling power output equivalent to 70% of the baseline IWRT P_{peak}^t value.

5.2.3 Outcome measures and analysis

The following outcome variables were examined during the CWRT:

P^t : the total mechanical work rate.

$\Delta\dot{V}_{\text{O}_2}$: the increase in \dot{V}_{O_2} above passive \dot{V}_{O_2} .

O₂ cost: the total oxygen cost of work.

η : the total work efficiency.

\dot{V}_E/\dot{V}_{O_2} : the ratio of \dot{V}_E to \dot{V}_{O_2} .

RER: the ratio of the \dot{V}_{CO_2} to \dot{V}_{O_2} .

La^- : blood lactate concentration.

$stim/P^t$: the electrical cost of work.

RER_{high}: the highest RER value of a 60 sec rolling average during the exercise phase.

Mean values were calculated for each variable and these were taken as the average over the last 5 min of the exercise phase of the CWRT.

Data were also obtained for thigh muscle and fat CSA by pQCT at each test point. Measurements were taken bilaterally at 25% of total bone length, measured from the knee joint gap (with permission from A. Frozler, Swiss Paraplegic Research, CH-6207 Nottwil, Switzerland). The test protocol is fully explained in [51].

The theoretical framework underpinning the novel efficiency calculations used here, appropriate for those with severe physical impairment, is fully explained in [85] and briefly detailed here. The O_2 cost of FES cycling was calculated as follows:

$$O_2 \text{ cost} = \frac{\Delta \dot{V}_{O_2}}{P^t} \text{ [mL/min/W]} \quad (5.1)$$

Efficiency was calculated as the *total work efficiency*, η_w^t i.e. the ratio of the total mechanical work rate and the approximate net energetic cost of the exercise (i.e., the energetic cost during cycling minus the cost during passive cycling):

$$\eta_w^t = \frac{P^t}{P^{in} - P^p} \times 100\% = \frac{P^t}{(\dot{V}_{O_2}^{in} E^{in} - \dot{V}_{O_2}^p E^p)} \times 100\% \quad (5.2)$$

Here, P^{in} represents the total metabolic work measured and P^p , the metabolic work of passive exercise. $\dot{V}_{O_2}^{in}$ is the average oxygen uptake rate during steady-state exercise over a given time interval and $\dot{V}_{O_2}^p$ is the average oxygen uptake rate during steady-state passive cycling. E^{in} and E^p denote the energy equivalents of the oxygen in each state (exercise or passive, respectively). The approximate energy equivalents are taken to be in the range 19.59–21.14 $\text{kJ} \cdot \text{l}^{-1}$, and are normally derived from the RQ where an RQ of 0.7 corresponds to an energy value of 19.59, an RQ of 1.0 has an energy value of 21.14, and intermediate values are obtained by linear interpolation. However, it should be noted that during transcutaneous nerve stimulation, aerobic and anaerobic motor units are recruited in a simultaneous, synchronous and non-selective manner, even at very low work rates [69]. This will result in an anaerobic energy contribution to work that is not accounted for by the equation. Accordingly, the term

RER is used here in place of RQ to reflect this uncertainty, where there will be a possible underestimate of energy equivalents and a resultant overestimate of efficiency values.

The electrical cost of stimulation, the stim/P^t , was also calculated. See section 3.4.1 for full details.

5.2.4 Statistical analysis

Using *Minitab 13* software (Minitab Inc., USA) all data were examined for normality of variance and distribution (Anderson Darling test) and were not found to be different from normal ($P > 0.05$). Paired t -tests (2-tailed) were performed between consecutive tests and baseline values. Multiple Pearson product-moment correlations were run between possible confounding variables and where associations were significant and relevant, a regression analysis or general linear model (GLM) was then performed. Significance level was regarded as ($P \leq 0.05$). Absolute and delta values are expressed as means \pm SD.

5.3 Results

5.3.1 The oxygen cost and efficiency of work

The O_2 cost and the corresponding efficiency estimates after 6 months ($P = 0.79$ and $P = 0.74$ respectively) and 12 months of training ($P = 0.77$ and $P = 0.83$ respectively) were not significantly different from pre-training values (see table 5.1). Individual efficiency values ranged from 4–10% prior to training, to 4–15% after 12 months.

5.3.2 The electrical cost of work

There was a significant reduction ($P = 0.008$) in the stim/P^t ratio over the course of training which equated to a mean relative reduction of 37% (this ranged from a reduction of 59% to an increase of 3%). Most of this change, equating to a mean relative reduction of 32%, occurred during the first 6 months ($P = 0.017$). (Table 5.1). After 6 months of training, a positive relationship was found between absolute stim/P^t and O_2 cost values ($r^2 = 0.54$, $P = 0.025$), and just under half of the variance in stim/P^t values was accounted for by thigh fat CSA ($r^2 = 0.44$, $P = 0.038$). None of these variables were found to be related prior to training.

After 12 months of training absolute stim/P^t were values were positively related to fat CSA values ($r^2 = 0.66$, $P = 0.007$) (Fig.5.1). No other significant associations were found between variables after 12 months.

5.3.3 Individual changes in energetics variables

None of the changes in energetics values over the first 6 months were associated with changes in any other measured variable. Between 6 and 12 months, changes in O_2 cost were closely

Table 5.1: A summary of the constant work rate test results

Outcome variables	N	0 months	N	6 months	N	12 months
\overline{P}^t , W	10	5.8 ± 3.0	11	4.8 ± 2.1	10	4.7 ± 2.2
$\Delta \dot{V}_{O_2}$, mL/min	10	214 ± 99	9	172 ± 79	9	174 ± 97
O ₂ cost, mL/min/W	10	38.4 ± 14.5	9	36.9 ± 16.7	9	40.14 ± 17.3
η , %	10	7.7 ± 2.2	9	8.6 ± 3.1	9	8.1 ± 3.6
\dot{V}_E/\dot{V}_{O_2} , L/min	11	32.9 ± 5.3	11	$\dagger 30.3 \pm 2.9$	10	31.6 ± 4.2
RER	11	0.98 ± 0.13	11	0.90 ± 0.12	10	0.94 ± 0.08
highest RER	11	1.12 ± 0.15	11	1.02 ± 0.17	10	1.07 ± 0.13
La ⁻ , mmol/L	9	5.1 ± 1.2	11	$\dagger 3.2 \pm 1.2$	11	3.7 ± 1.4
stim/ P^t , $\mu C/\text{min}/W$	9	12.31 ± 5.35	10	$\dagger 8.78 \pm 5.58$	9	$\dagger 8.18 \pm 3.7$

Data are absolute mean values \pm SD. Values were not established for all subjects for all variables due to technical difficulties. Values are the average over the last 5 min of exercise, except for highest RER which was the highest of a 60 sec rolling average over the course of the exercise. Paired *t*-tests were performed between each consecutive test and between each test and baseline. * Significantly different from preceding test-point or † from baseline at $P \leq 0.05$.

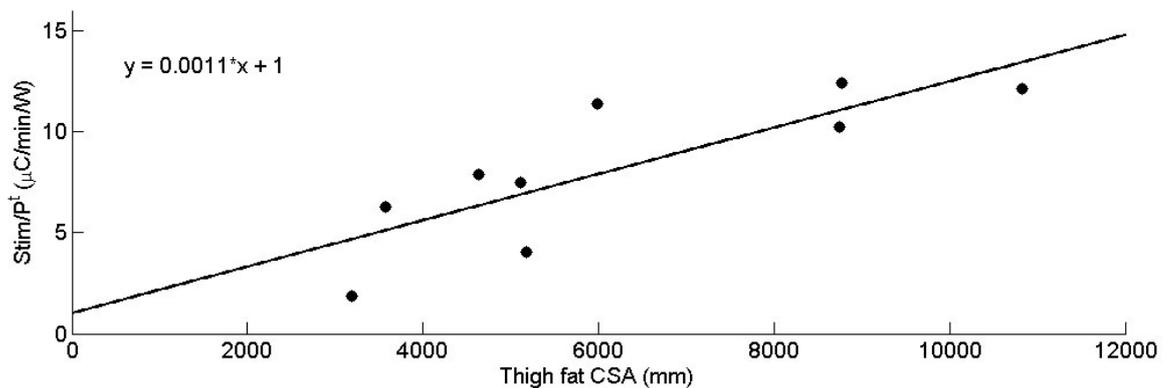


Figure 5.1: Regression plot showing the significant relationship between absolute thigh fat CSA values and stim/ P^t after 12 months of training ($n = 9$, $r^2 = 0.66$, $P = 0.007$).

related to changes in stim/ P^t ($r^2 = 0.84$, $P = 0.001$) (Fig.5.3), and changes in stim/ P^t were in turn, related to changes in thigh fat CSA ($r^2 = 0.53$, $P = 0.026$) (Fig.5.2).

5.3.4 Markers aerobic and anaerobic metabolism

The \dot{V}_E/\dot{V}_{O_2} had reduced after 6 months ($P = 0.036$), but was not different from pre-training values after 12 months ($P = 0.59$). There was also a significant reduction in La after 6 months ($P = 0.006$) which just failed to reach significance by 12 months ($P = 0.069$). The RER and the highest RER value tended to reduce after 6 months ($P = 0.082$ and $P = 0.087$ respectively) but remained no different from baseline values after 12 months ($P = 0.27$ and

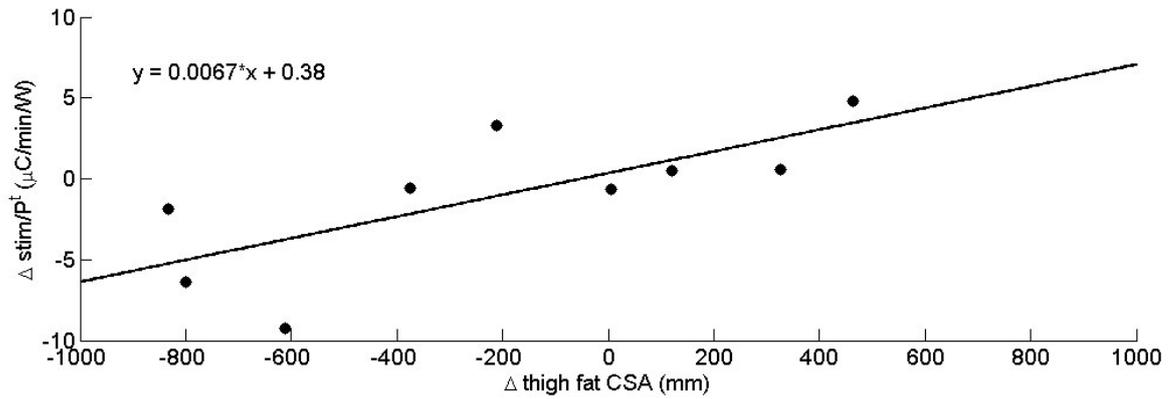


Figure 5.2: Regression plot showing the significant relationship between (Δ) thigh fat CSA and Δ stim/ P^t between 6 and 12 months ($n = 9$, $r^2 = 0.53$, $P = 0.026$).

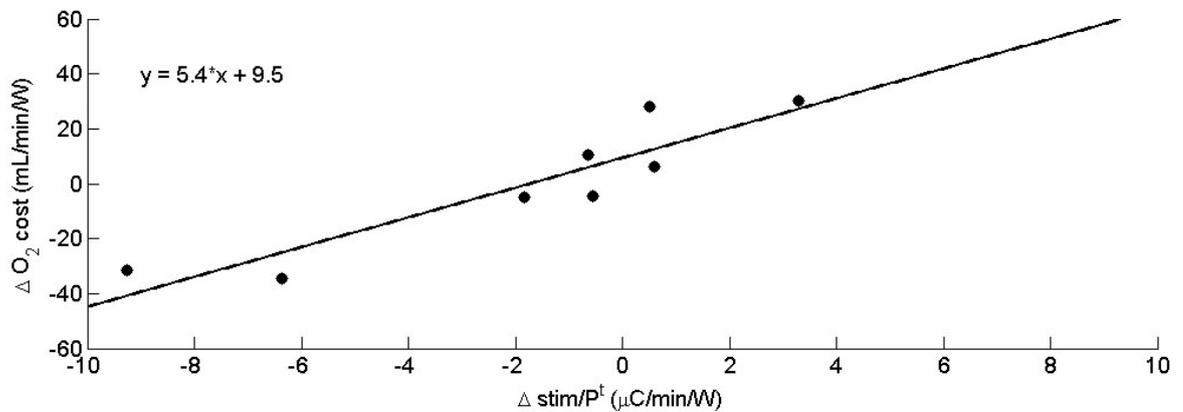


Figure 5.3: Regression plot showing the significant relationship between the magnitude of change (Δ) in stim/ P^t and Δ O₂ cost that occurred between 6 and 12 months of training ($n = 8$, $r^2 = 0.84$, $P = 0.001$).

$P = 0.26$ respectively) (Table 5.1). The changes in RER and RER_{high} that occurred between 6 and 12 months were positively related to changes in stim/ P^t ($r^2 = 0.56$, $P = 0.020$ and $r^2 = 0.62$, $P = 0.011$ respectively).

5.4 Discussion

5.4.1 Adaptations in response to training

The aim of this investigation was to investigate the energetic and metabolic adaptations to 12 months of high-volume FES cycle training for the first time. Here it was found that there was no significant mean difference in the O₂ cost of work or efficiency at any time during or after the training period. O₂ cost and efficiency varied substantially between subjects, as did any individual changes in value between tests: efficiency estimates varied between 4 and

15% and between 6 and 12 months, the magnitude and direction of individual changes in O_2 cost were related to the magnitude and direction of changes in stim/P^t , which were in turn linearly related to changes in thigh fat CSA. There was also a significant correlation found between changes in RER and RER_{high} , and changes in stim/P^t over this time. There were, nonetheless, significant reductions in stim/P^t , \dot{V}_E/\dot{V}_{O_2} and La^- over the first 6 months of training, but these were not associated with changes in any other measured variable. The absolute stim/P^t values at 6 and 12 months were positively related to thigh fat CSA and, at 6 months only, with O_2 cost.

5.4.2 Mechanical effectiveness

In this study, the power required for the motor to turn the passive, non-stimulated legs was quantified as internal work in the efficiency calculations [85]. Nonetheless, it is possible that only a certain proportion of the muscular contractions elicited by ES will produce useful measured work at the pedals. Although there was no direct evidence of counteractive, antagonistic co-contractions (via depolarisation of the antagonistic motor nerves by the ES field, or by myotactic reflex spasms) during the tests, it is possible that some of the work may have been *wasted* due to biomechanically unfavourable agonist and synergist stimulation on/off angles [62].

Accordingly, the internal work values used in the calculations may underestimate the muscular work *actually* performed whilst rotating the pedals by ES, and result in low efficiency estimates. This poor mechanical effectiveness (if a constant consequence of the ES paradigm employed) is likely to occur regardless of whether the stimulated muscle mass is paralysed and atrophied, or healthy and fit [98] and could explain, in part, the continued low efficiency of FES cycling, even after training.

5.4.3 Muscle adaptation and the electrical cost of work

As expected, there was no relationship found between total thigh muscle CSA and any of the energetics measures; the CWRTs were conducted at sub-maximal intensities, which did not rely on the total muscle CSA for power production. Nonetheless, significant increases in P_{peak}^t (see previous chapter) and in thigh muscle CSA were found over the first 6 months of the study [57]. This provides a logical explanation for the significant decrease in the stim/P^t that was found over this time, in the absence of any significant change in O_2 cost; a greater muscle mass would have been available for power production per motor unit stimulated in the hypertrophied muscle, resulting in a reduction in the level of stimulation required to activate the same absolute muscle mass and to produce the same absolute power output. In the absence of fibre type transformation that would affect ATP turnover rate, then O_2 cost would be expected to remain very similar.

5.4.4 Thigh fat CSA and the electrical cost of work

The relationship between absolute stim/P^t values and thigh fat CSA found at 6 and 12 months illustrates the significant effect of tissue impedance on the power-cost relationship. Higher impedance (thigh fat CSA) required a higher level of stimulation charge to depolarise the agonist motor nerve, resulting in a wider electrical field being generated. It is then possible that more motor units were consequently and unnecessarily stimulated, regardless of whether they were agonistic, synergistic or antagonistic and this may explain the positive relationship found between stim/P^t and O_2 cost.

This would also explain the relationship found between the magnitude and direction of changes fat CSA and in the stim/P^t , and changes in stim/P^t and energetics measures during the last 6 months of training (after the time during which all other significant metabolic training adaptations had occurred), and highlights the significant effect of underlying fat tissue on impedance and on the subsequent electrical and metabolic cost of this type of exercise.

5.4.5 Anaerobic adaptations

The reduction in the $\dot{V}_E/\dot{V}_{\text{O}_2}$ over the first 6 months of training may suggest improvements in oxygen transport and/or extraction at the tissue level. However, since values remained significantly higher than the normal value of about 27 ($P < 0.05$) [173]), and the highest RER remained at above 1 after training, then values are more likely to reflect the \dot{V}_E required to eliminate the \dot{V}_{CO_2} from the buffering of lactic acid (HLA). This is supported by the significant mean reduction in blood La^- accumulation that was observed over this time, and the slight tendency for mean and highest RER to reduce. These changes would suggest that although there was still a relatively high anaerobic contribution to work, there were proportionately greater improvements in blood La^- transport and clearance capacity than in its production [63]. Additionally, these findings may suggest improvements in humoral pH buffering and in CO_2 storage capacity.

5.4.6 Fibre type recruitment

These findings, in combination with the fatigue resistance that was observed over the course of the training programme, provide evidence of a fibre type transformation from fatigable FG towards more fatigue resistant FOG isoforms, rather than towards SO isoforms [38]. These adaptations, in addition to the non-physiological, disordered recruitment of motor units normally observed during ES [69] will influence total work efficiency: there is an inherent inefficiency with this type of metabolic coupling, where FG fibres are recruited to contract synchronously from the outset. Fast fibres, regardless of whether glycolytic or oxidative, will produce La^- , even in the presence of oxygen, and they are also likely to retain their high and

costly glycolytic ATP turnover rate [2, 63]. This was evidenced here by the relatively high \dot{V}_{O_2} and RER values attained at such low work rates, and by the high O_2 cost of work, even after training.

This, and the observation that efficiency values were not found to be different between stimulated healthy, fit leg muscles and paralysed, atrophied muscles, supports the notion that it is the stimulation paradigm itself that is the source of inefficiency, and not the chronic effects of paralysis.

The linear relationship found between the changes in both the mean and highest RER values and changes in stim/P^t over the last 6 months of training suggest that there is a quantitative link between the CSA of the predominantly fast muscle that is stimulated per unit of power produced, and stim/P^t . This, in addition to the relationship also found between stim/P^t and O_2 cost, would suggest that changes in the O_2 cost of work and therefore the estimated efficiency measures, related to changes in the number of motor units stimulated per unit of power produced, than to any change in the efficiency of internal metabolic coupling per se.

5.5 Conclusion

For this relatively small group of SCI individuals, high-volume FES cycle training did not significantly improve cycling efficiency at any time during or after training with efficiency estimates ranging from only 4% up to 15%. However, metabolic adaptations had occurred by 6 months that permitted a significant reduction in stim/P^t and improvements in anaerobic capacity. After 6 months, by which time all significant metabolic adaptations to training had occurred, the absolute values of, and the magnitude and direction of change in thigh fat CSA and consequently in stim/P^t , explained the individual changes in O_2 cost of work that occurred during this time. These findings, suggest that for this group the metabolic cost and therefore the corresponding efficiency of FES cycling related primarily quantitatively, to degree of muscle mass stimulated per unit of power produced, rather than qualitatively to the metabolic status of the muscle. The electrical cost of work appeared to be determined by the motor unit size and to the level of tissue impedance caused by the subcutaneous fat layer. Controlling for these observed sources of variance, future investigations are recommended that include larger subject groups, to examine work efficiency estimates at higher relative work rates and different pedalling cadences, and for other non-cyclical ES exercise. This would provide further interesting insights into the energetics of this unique type of exercise.

Chapter 6

Metabolic gas exchange thresholds: a paradigm of volitional exercise?

The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them.

Sir William Bragg

The physiological basis of the metabolic threshold analysis paradigm is briefly examined in this chapter. This is followed by an investigation into the existence of such thresholds during incremental, electrically stimulated cycling tests. The effect of training on the appearance of these thresholds is discussed and, based on these findings, the validity, and utility of metabolic threshold analysis as a tool for exercise intensity prescription in FES cycling is critically discussed. This work forms the basis of a journal article that is in preparation and detailed as follows:

H.R. Berry, T.H. Kakebeeke, N. Donaldson, D.B. Allan and K.J. Hunt. The aerobic gas exchange threshold: a paradigm of volitional exercise? *Medicine and science in sports and exercise*, in preparation.

6.1 Introduction

Although $\dot{V}_{O_{2\max}}$ testing is the most frequently used method for identifying the upper reaches of aerobic capacity, the methods employed require subjects to be highly motivated and to give a maximal effort. Such tests may lack measurement precision at high intensities and can fail to identify small but important changes in endurance capacity, especially in diseased or disabled subjects [117]. Metabolic threshold analyses can provide valuable and reliable indications of the work intensities at which the anaerobic contribution to work becomes measurable, and the intensities up to which aerobic endurance can be sustained. These

thresholds can be assessed either invasively by blood sample analysis, or non-invasively by an analysis of pulmonary gas exchange at the mouth. Metabolic threshold analyses have been used successfully as effective, analytical tools and for volitional exercise prescription in clinical, scientific and sports training settings [92]. Periods of exercise training have been found to delay the appearance of these thresholds, resulting in increased work and endurance capacity. The GET and its response to training is also strongly influenced by genetics [117].

6.2 Metabolic threshold analysis

In the 1920s, Hill and colleagues recognised that as exercise intensity increased beyond a certain level, proportionately more energy was produced by anaerobic metabolism [12]. This is consistent with the orderly Henneman motor unit recruitment principle, whereby as the work rate increases, motor units are progressively recruited according to the size principle from small, low threshold, oxidative units up to larger, higher threshold, progressively more glycolytic, units [50]. This results in an increase in the conversion of pyruvic acid (formed during glycolysis) to HLa, leading to a measurable increase of the glucose metabolite La^- in the blood. The dissociated protons (H^+) cause an acceleration in \dot{V}_{CO_2} giving a landmark indicator of metabolic status and, therefore, of endurance capacity at a given intensity of work or \dot{V}_{O_2} [17, 117].

6.2.1 Blood lactate analysis

HLa is more than 99% dissociated into H^+ and La^- ions at physiological pH (pH 7.4). Both ions are transported out of the cell and into the blood by a co-transporter where depending on the acid-base equilibrium, H^+ is buffered by plasma proteins, especially deoxyhaemoglobin (Hb^-) and bicarbonate (HCO_3^-) [63]. La^- , bound to sodium (Na^+), is transported to other cells and tissues as a valuable fuel source for immediate oxidation, or to the liver where it is converted to glucose and glycogen (gluconeogenesis) via the cori cycle. It is thought that as adequate O_2 becomes available during recovery from exercise or as exercise intensity reduces, then most of the lactate formed (75-80%) is oxidised back to pyruvate by the reversible actions of lactate dehydrogenase, providing a substrate for oxidative metabolism [115]. La^- is produced by FOG and FG muscle fibres, even in the presence of adequate O_2 , due to their high glycolytic enzyme activity, their paucity of mitochondria and their lactate dehydrogenase isoform that favours lactate formation over pyruvate reconversion [20].

Aerobic lactate threshold

The corresponding \dot{V}_{O_2} value at the first increase in the level of La^- measured in capillary blood during an IWRT of ≥ 4 -min work rate increments [113] has often been regarded as the aerobic lactate threshold. Small increases in workload close to this intensity produce small,

non-exponential increases in La^- [176]. Values of about 2.0 mmol/L to 2.5 mmol/L [113, 163], or less than 1.0 mmol/L [115] above resting levels are used to determine the corresponding \dot{V}_{O_2} at this transitional threshold.

Anaerobic lactate threshold

When La^- and H^+ production and release into the bloodstream outweighs uptake or buffering capacity, equilibrium or lactate steady state is lost and lactate levels are seen to rise exponentially from levels of about 4.0 mmol/L, signalling the anaerobic lactate threshold or onset of blood lactate accumulation (OBLA) [115]. This work rate at this threshold, sometimes termed the maximal lactate steady state (MLSS) or critical power level [76], is thought to represent the maximum exercise intensity that can be sustained for a prolonged period of time. Beyond this point, metabolic acidosis disrupts contractile function and enzyme activity, and exercise becomes increasingly more difficult to sustain [117, 94].

La^- levels in the blood reflect the balance between total systemic La^- accumulation and clearance, but not specific clearance inadequacies due to local muscular haemodynamics, or an imbalance between the rate of glycolysis and mitochondrial respiration in specific muscles [115].

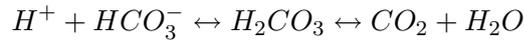
This two threshold model has been substantiated by many studies using CWRTs of 30-45 min duration, but the La^- concentration criterion of 2 and 4 mmol/L have been found to over or under represent the thresholds in some individuals and to be influenced by the muscle mass employed and by nutrient status [173, 115, 117].

6.2.2 Respiratory gas exchange analysis

The metabolic thresholds indicated by increased capillary lactate measures can also be determined non-invasively by analysis of ventilation and of pulmonary gas exchange [172, 174, 17]. These are best determined from a continuous graded exercise test consisting of small work rate increments every minute. Interpretation of such data can be difficult where data is unduly ‘noisy’ or when relating to diseased or unfit subjects [163].

During incremental exercise, the body fluid acid-base balance is disrupted by a combination of factors including the strong ion concentration balance (sodium (Na^+) + potassium (K^+) + calcium (Ca^{2+})) – (chloride (Cl^-) + lactate (La^-)) [63] and increased H^+ levels as the ATP consumption to regeneration ratio is exceeded [165]. When the acid buffering capacity of plasma proteins is exceeded, there is an increase in \dot{V}_{CO_2} as the H^+ , dissociated from La^- , is then buffered by HCO_3^- to form H_2CO_3 (carbonic acid), which dissociates to form CO_2 and H_2O in the presence of the enzyme carbonic anhydrase [176] This is described

by the following reversible chemical reaction:¹



This results in an excess \dot{V}_{CO_2} in relation to \dot{V}_{O_2} , which can be detected by observation of the breath by breath pulmonary gas exchange.

Aerobic gas exchange threshold

The excess \dot{V}_{CO_2} in relation to \dot{V}_{O_2} is normally evident as a nonlinear increase in \dot{V}_E or \dot{V}_{CO_2} , or a disproportionate increase in the ratio of ventilation to \dot{V}_{O_2} : the slight increase in CO_2 partial pressure in the blood is detected by the carotid bodies which then stimulates a compensatory increase in ventilatory drive to match CO_2 production [174]. This metabolic phenomenon represents the equivalent of the aerobic lactate threshold but is sometimes termed the aerobic gas exchange threshold [96, 117] or period of isocapnic buffering [173], often also referred to as the ventilatory or anaerobic threshold [174]. It occurs most often at about 50-60% of $\dot{V}_{O_{2max}}$ and represents the boundary between moderate and heavy intensity exercise. The term gas exchange threshold (GET) is now commonly used in the literature [102, 93, 97] and will be used here.

Many criteria have been suggested in the literature to determine the GET, such as: the first rise in the ventilatory equivalent for O_2 (\dot{V}_E/\dot{V}_{O_2}) without a concomitant increase in the ventilatory equivalent for CO_2 (\dot{V}_E/\dot{V}_{CO_2}); an increase in the expiratory fraction of O_2 as a consequence of CO_2 driven hyperventilation or *hyperpnea*; and an increase in the RER beyond unity [42, 174].

These criteria have normally been determined by visual observation and are subject to a great deal of reviewer variability: Yeh *et al.* concluded that visual identification of evidence of an increased lactate production from noninvasive gas responses was not suitable for clinical use due to inter-reviewer variation of 16% [180]. However, attempts have been made to automate the processes [130, 17, 96, 151], with variable outcomes.

An upward deflection in the linear relationship between both of the metabolic gases, termed the V-slope by Beaver *et al.* [17], has been suggested as being the most reliable metabolic marker for the aerobic threshold, since detection is not affected by ventilatory variance as can be seen in subjects with impaired ventilatory chemoreception.² [163, 176, 117], or by other factors which could affect ventilation such as rising catecholamine or ammonium levels which can occur at about 50% of $\dot{V}_{O_{2max}}$ [163, 115].

Beaver *et al.* [17] used a computerised regression analysis of the slopes of \dot{V}_{CO_2} (y-axis) and \dot{V}_{O_2} (x-axis) to determine the onset of excess CO_2 production from buffering of H^+ ,

¹For simplicity, the sodium ion exchange between sodium bicarbonate and sodium lactate has not been included.

²Reception of changes in CO_2 that drives ventilation in normoxic conditions [50].

where they found that the first upward deflection in linearity corresponded closely with the measured lactate threshold.

The effect of body CO_2 storage capacity on \dot{V}_{CO_2} can also affect the time course for the appearance of this threshold and there is a possibility of a hyperventilation induced alteration of body CO_2 stores at the start of incremental exercise that could result in a false, delayed threshold measure due to a CO_2 wash-in to depleted body stores [131].

Examination of the RER during incremental work has been shown disputably [174, 155] to be a satisfactory marker of the aerobic gas exchange threshold, dependent on work duration, but does not identify the precise point at which the ratio starts to increase disproportionately. Nonetheless, it is possible that changes in substrate usage during an IWRT, which will affect the RER, could be misinterpreted as the appearance of non-metabolic CO_2 production.

Anaerobic gas exchange threshold

A second threshold, the respiratory compensation point (RC), normally occurs at about 80-90% of $\dot{V}_{\text{O}_{2\text{max}}}$ and is apparent as a hyperventilation disproportionate to \dot{V}_{CO_2} . This threshold relates to the MLSS and results from respiratory compensation for metabolic acidosis: bicarbonate buffering capacity in the blood becomes saturated and no more excess CO_2 can be produced. The decrease in blood pH is sensed by the carotid bodies which stimulate an increase in ventilation. The CO_2 pressure gradient increases down and away from the blood to the alveoli and causes a reduction in end-tidal CO_2 pressure and a reduction in blood pH. This increase in the $\dot{V}_{\text{E}}/\dot{V}_{\text{CO}_2}$ also causes an increase in $\dot{V}_{\text{E}}/\dot{V}_{\text{O}_2}$ with a concomitant increase in expiratory O_2 tension. This threshold demarcates the heavy and severe exercise intensity domains and work capacity beyond this point is very limited [92, 117].

Hyperventilation attributable to other reasons such as psychogenic hyperventilation, hypoxemia, pain, rising catecholamine or ammonium levels that can also occur at lesser exercise intensities ($\sim 50\%$ of $\dot{V}_{\text{O}_{2\text{max}}}$) is sometimes erroneously attributed to this respiratory compensation point, indicating the multifactorial nature of ventilatory control which could affect the validity of ventilatory threshold analysis as a true marker of metabolic acidosis [163, 117].

6.2.3 Metabolic thresholds and electrically stimulated exercise

The concept of a gradual shift from a predominantly oxidative energy metabolism toward a mixed oxidative-glycolytic metabolism during progressive, incremental work rate ES exercise is unlikely: transcutaneous ES motor unit recruitment does not follow the normal orderly size principle found during volitional exercise [69] (see section 1.3.2). ES motor unit recruitment is more random and determined by a combination of charge level, axonal diameter [165], the extent of axonal branching, nerve fibre geometry within the muscle, tissue impedance

and motor unit type predominance [100, 53]. Recruitment is synchronous and of spatially fixed, nonspecific motor units. The proportion of energy supplied by anaerobic pathways will be proportionate to the number and size of FOG and FG fibres within the recruited motor units: after spinal cord injury (SCI), muscle fibres lose their aerobic capacity and tend to atrophy and transform to a primarily FG phenotype [139]. Accordingly, there is likely to be an anaerobic contribution to energy production from the initiation of the first muscular contraction.

To date, there have been no metabolic gas exchange threshold analyses performed during ES exercise that could provide evidence of this recruitment theory from a metabolic perspective. The test bed that has been available to researchers to date has lacked the measurement precision and temporal resolution required to identify the precise workload and cardiorespiratory stress at which the anaerobic contribution to exercise becomes measurable. Accordingly, the effects of 12 months of cycle training on the appearance of the GET will be examined using a novel sensitive IWRT protocol; in a pilot study using this protocol, it has been demonstrated that it is, in principle, possible to detect a GET in a trained SCI subject performing FES cycling [55]. The utility of this exercise test parameter as a marker of exercise endurance capacity and a valid prescriptive tool for this ES exercise with individuals with paraplegia will be discussed.

6.3 Methods

Please refer to chapter 3 for a full and detailed description of the methods and statistical analysis employed. Methods peculiar to this part of the study are given below.

6.3.1 Subjects

11 subjects were studied and are detailed in full in Table 3.1 on page 38. For one subject (no. 5) the IWRT failed to elicit a measurable GET, or an RER in excess of unity during any test. His data are therefore not included in the analysis here.

6.3.2 Exercise testing and analysis

An IWRT was performed prior to cycle training and after 12, 26, 39 and 52 weeks of training. The following parameters were determined from these tests:

\dot{V}_{O_2} at GET: The GET was calculated from edited, but not averaged (unsmoothed) \dot{V}_{CO_2} and \dot{V}_{O_2} values to retain a high degree of temporal resolution [147]. The V-slope method [17] was employed, using a computerised linear regression model. The results were corroborated by comparing values against other gas exchange parameters including the \dot{V}_E/\dot{V}_{O_2} and \dot{V}_E/\dot{V}_{CO_2} vs. \dot{V}_{O_2} , and O_2 and CO_2 end tidal pressures vs. \dot{V}_{O_2} [173, 55].

GET as percentage of $\dot{V}_{O_2\text{peak}}$: The relative exercise intensity at which the GET appears was calculated by expressing the GET as a percentage of the $\dot{V}_{O_2\text{peak}}$. The methods for $\dot{V}_{O_2\text{peak}}$ determination and the values for each test-point are presented in chapter 4. It should be noted that due to the level of data ‘noise’, $\dot{V}_{O_2\text{peak}}$ values were calculated over a 60 sec rolling average (low temporal resolution), and the GET values here are estimated from non-averaged \dot{V}_{O_2} data (high temporal resolution) [147] (a full explanation for this data treatment is given in 2.2.1). This will result in percentage values that may be disproportionately high.

\dot{V}_{O_2} at RC: This was determined by first finding the \dot{V}_{CO_2} value at the point of deviation from linearity in the \dot{V}_{CO_2}/\dot{V}_E plot. The corresponding \dot{V}_{O_2} was then determined by examining the $\dot{V}_{O_2}/\dot{V}_{CO_2}$ and the \dot{V}_{O_2}/\dot{V}_E plots. The RC values were also calculated from un-smoothed data but are not presented here relative to $\dot{V}_{O_2\text{peak}}$ since they often exceeded the 60 second averaged $\dot{V}_{O_2\text{peak}}$ values.

Power at GET: The cycling work rate at the GET was determined from the \dot{V}_{O_2} /work rate relationship.

The dynamic oxygen cost: The dynamic oxygen cost, determined over the linear phase of the \dot{V}_{O_2} /work rate relationship, was defined as $\Delta\dot{V}_{O_2}/\Delta P^t$, where $\Delta\dot{V}_{O_2}$ represents the increment in \dot{V}_{O_2} arising from an increment in ΔP^t .

La^-/P_{peak}^t : The blood lactate value from a sample taken 1 min after the end of the ramp phase was expressed relative to the P_{peak}^t produced during the test. See chapter 3 for details of blood sampling methods and analysis.

6.3.3 Statistical analysis

See chapter 3 for details of statistical analysis employed.

6.4 Results

Table 6.1 summarises the IWRT outcomes under investigation here. Due to technical difficulties, not all data sets were complete and, therefore, the number of paired values (n) used in each paired t -test are given where appropriate in the text.

6.4.1 The GET

Prior to cycle training, the GET was detected at a \dot{V}_{O_2} of 351 ± 103 ml/min (mean \pm SD) (Table 6.1). The \dot{V}_{O_2} values at GET were not found to be significantly different after 3 months ($n = 8, P = 0.18$), 6 months ($n = 7, P = 0.11$), 9 months ($n = 8, P = 0.87$) or 12

Table 6.1: Summary of incremental work rate test outcome measures.

Outcome variables	0 months	3 months	6 months	9 months	12 months
GET \dot{V}_{O_2} , ml/min	351 \pm 103	388 \pm 56	409 \pm 108	368 \pm 97	392 \pm 110
GET % of $\dot{V}_{O_{2peak}}$	64.7 \pm 10.6	61.0 \pm 15.7	*54.1 \pm 8.1	*48.7 \pm 11.2	*49.2 \pm 13.5
WR at GET, W	3.86 \pm 1.76	4.64 \pm 1.38	4.16 \pm 2.63	4.64 \pm 2.05	4.27 \pm 2.26
RC point, ml/min	535 \pm 107	623 \pm 196	†774 \pm 248	762 \pm 258	744 \pm 189
$\Delta\dot{V}_{O_2}/\Delta P^t$, ml/min/W	19.9 \pm 12.9	22.8 \pm 10.8	27.0 \pm 9.9	21.0 \pm 7.6	23.7 \pm 10.4
La^-/P^t_{peak} , mmol/L/W	0.44 \pm 0.18	0.43 \pm 0.19	0.43 \pm 0.32	*0.33 \pm 0.12	0.39 \pm 0.19

Data are absolute mean values \pm SD. Values were not established for all subjects for all variables at each test point due to technical difficulties. Two-tailed paired t -tests were performed between each consecutive test and between each test and baseline (see main text for n compared at each test point). *Significantly different from pre-training values, or †, from previous test-point at $P \leq 0.05$.

months ($n = 8, P = 0.15$) of training. Figure 6.1 shows the ventilatory and gas exchange parameters used to establish the RC and GET for 1 typical subject after 6 months of training.

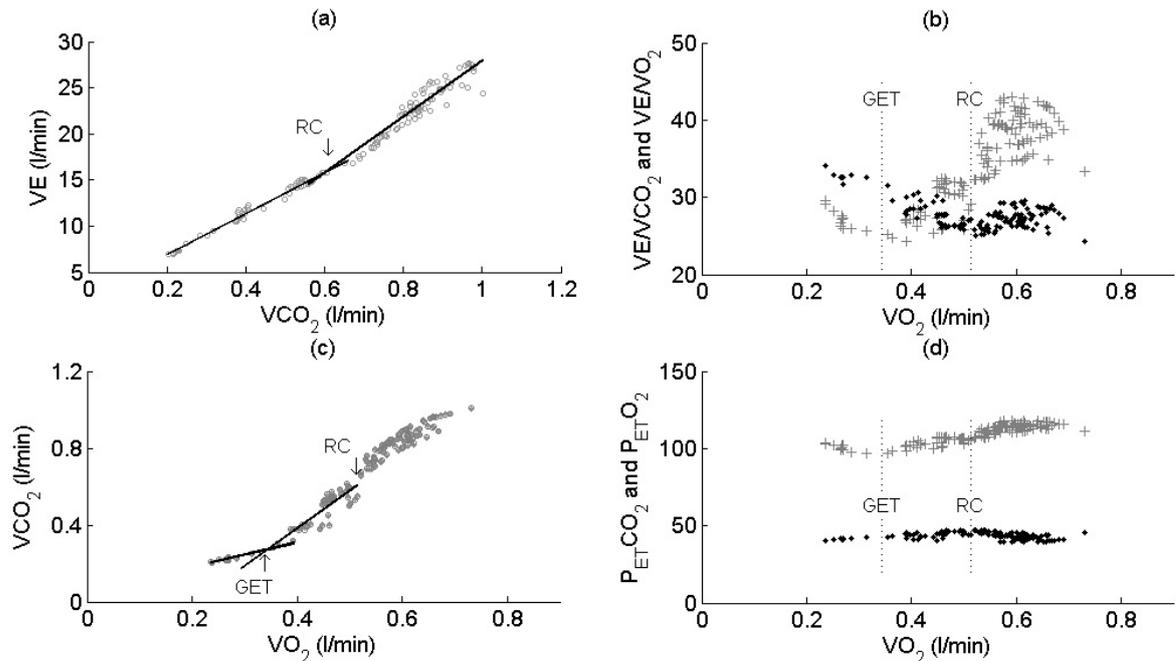


Figure 6.1: Representative plots for one subject showing the aerobic gas exchange threshold (GET) and the respiratory compensation (RC) point for metabolic acidosis after 6 months of training. (a) shows the RC point as a hyperventilation with respect to \dot{V}_{CO_2} . Data beyond this point was then eliminated from the V-slope analysis (c). (b) shows the ventilatory equivalents for both \dot{V}_{O_2} (+, grey) and \dot{V}_{CO_2} (•, black) plotted against \dot{V}_{O_2} and (d) shows the end tidal gas pressures for both CO_2 (•, black) and O_2 (+, grey). The RC point, and the GET determined from the V-slope analysis are indicated on the plots where appropriate.

The GET, expressed as a percentage of $\dot{V}_{O_{2peak}}$, was found to be 64.7 ± 10.6 % at baseline. This had decreased after 6 ($n = 7, P = 0.02$), 9 ($n = 8, P = 0.016$) and 12 months of training

($n = 8, P = 0.02$) (Table 6.1).

The GET was found at a work rate of 3.86 ± 1.76 W and this was not significantly different after 3 months ($n = 8, P = 0.10$), 6 months ($n = 7, P = 0.44$), 9 months ($n = 8, P = 0.45$) or 12 months ($n = 8, P = 0.70$) of training (Table 6.1).

6.4.2 The RC point

This parameter was only detected for 9 subjects during tests. See table 6.1 for mean values and table 6.2 for absolute values. Prior to cycle training, an RC point was detected in only 4 of the subjects. For these 4 subjects, there was no significant difference in RC values after 3 ($n = 4, P = 0.18$), or 6 ($n = 4, P = 0.104$) months, but by 9 and 12 months, only 2 data sets were available for comparison over time and were, therefore not statistically analysed. 7 data sets were able to be compared between 3 and 6 months, where it was found that the RC point had significantly increased ($n = 7, P = 0.04$). There were no differences between 6 and 9 months ($n = 5, P = 0.88$). Values ($n = 3$) between 9 and 12 months were not compared.

Table 6.2: Absolute \dot{V}_{O_2} values (mL/min) at the respiratory compensation (RC) point during the IWRTs. An RC point was not detected at any time for subjects 4 and 5.

Subject	Test point (months)				
	0	3	6	9	12
1	430	430	510	*	510
2	*	510	*	640	580
3	*	460	570	630	*
6	540	540	570	*	*
7	*	520	620	400	*
8	680	920	850	820	820
9	*	*	1130	*	950
10	*	910	1120	1120	860
11	490	690	820	960	*

6.4.3 Associated outcomes

The $\Delta\dot{V}_{O_2}/\Delta P^t$ value of 19.9 ± 12.9 ml/min/W (6.1) was not significantly different after 3 months ($n = 10, P = 0.44$) but had tended to increase over 6 months of training ($n = 10, P = 0.08$). Values after 9 months ($n = 10, P = 0.82$) and 12 months ($n = 10, P = 0.37$) were not significantly different from pre-training values (Table 6.1).

La^-/P_{peak}^t values were not different from pre-training values after 3 ($n = 9, P = 0.77$) and 6 ($n = 10, P = 0.96$) months, but by 9 months, the differences just reached significance ($n = 10, P = 0.05$). Differences between baseline and 12 months were not significant ($n = 10, P = 0.56$).

6.5 Discussion

This is the first study to investigate gas exchange thresholds during ES exercise in individuals with paraplegia and to examine the effects of training thereon. The GET, detected for all but one subject, occurred at very low work rates and at very low cardiorespiratory intensities, which remained unchanged even after 12 months of training. Where an RC point was identified, it was found to have significantly increased between 3 and 6 months of training but not thereafter. The relative GET, which represented a respiratory intensity 65% of $\dot{V}_{O_2\text{peak}}$ prior to training, became proportionately less over time, equating to only 49% of $\dot{V}_{O_2\text{peak}}$ after 12 months, by virtue of an increase in $\dot{V}_{O_2\text{peak}}$. The $\text{La}^-/P_{\text{peak}}^t$ values had reduced by 9 months, but by 12 months of training they were no different to pre-training values. In addition, the dynamic oxygen cost remained high throughout training, at about 3 times that normally found during volitional exercise (notwithstanding a slight tendency to for it to increase over the first 6 months).

6.5.1 The GET

Typically, the GET is found at a volitional exercise intensity of about 1.3 L/min in untrained healthy individuals, at about 1 L/min in chronically diseased individuals and at about 3.5 L/min in endurance trained individuals [117]. The GET, when expressed as a percentage of $\dot{V}_{O_2\text{peak}}$ or $\dot{V}_{O_2\text{max}}$, normally gives an indication of endurance capacity and of adaptations to endurance exercise: even where $\dot{V}_{O_2\text{peak}}$ or $\dot{V}_{O_2\text{max}}$ remain similar between individuals, or unchanged over time, the ability to sustain higher workloads over longer periods of time is normally determined by the percentage of $\dot{V}_{O_2\text{peak}}$ or $\dot{V}_{O_2\text{max}}$ at which the GET and RC occur. GET values of about 50–58% and RC values of $\sim 79\%$ have been reported for healthy sedentary adults, and of about 60% and 85–90%, respectively for trained (non-professional) cyclists [117].

Notwithstanding the slight over-estimate due to the calculation methods, the mean pre-training GET was found at 65% of $\dot{V}_{O_2\text{peak}}$, which is higher than would be expected for untrained individuals. However, when expressed in absolute terms, the GET exercise intensity of only 351 ml/min is extremely low and equates to the typical metabolic stress of a 70kg adult sitting playing cards, knitting or typing [115]. This \dot{V}_{O_2} is about one third of that normally found at the GET in untrained diseased patients during volitional exercise [117]. The appearance of the GET at such low work and cardiorespiratory intensities, even after a long period of endurance training, is consistent with the recruitment of FG fibres from the application of stimulation and the consequent early anaerobiosis elicited.

6.5.2 The dynamic oxygen cost

The dynamic oxygen cost was very variable between subjects, with values ranging from 7–42 mL/min/W prior to training, and 8–41 mL/min/W after 12 months of training (a CV of 65% and 44% respectively). The $\Delta\dot{V}_{O_2}/\Delta P^t$ during a volitional IWRT of 8–12, 1-min increments in work rate is normally linear and ~ 9 –11 mL/min/W for normal adults, with slight differences in slope and linearity being due to age, fitness level or disease. Variance was not found to be explained by age, lesion level nor time since injury for this group, but it is possible that differences in levels of thigh fat and in stimulation cost (not investigated here) may have accounted for some of the variance, similar to the findings in the previous chapter for the oxygen cost of constant work (chapter 5).

The consistently high dynamic oxygen cost found here is likely to reflect, in part, the oxygen cost of ATP replenishment in the FG fibres, which have a high ATP cost of force production (see chapter 1). These fibres are recruited, especially in SCI individuals where this fibre type predominates, regardless of ES exercise intensity. The findings would also indicate that fibres are unlikely to have transformed towards a SO phenotype, but towards more FOG fatigue resistant isoforms [106]. This finding is consistent with earlier observations that FES cycling is about 3 times more costly and more inefficient than volitional cycling [85] even after training (see chapter 5).

A 35% increase in thigh muscle cross sectional area (CSA) was recorded over the first 6 months of training and this did not significantly increase after this time [57]. Since hypertrophy is known to occur due to an enlargement of the existing muscle fibres within a motor unit [94], then a larger CSA of predominantly fast muscle would have been available for power production per motor unit stimulated. The associated momentary metabolic cost of power production in these inefficient fibres would be disproportionately high and may explain the tendency for the dynamic oxygen cost to have increased slightly over the first 6 months, notwithstanding any improvements in oxygen kinetics that may also have occurred [173].

6.5.3 Endurance capacity

The significant reduction in the GET as a percentage of $\dot{V}_{O_{2peak}}$ over time is contrary to what would be expected after a period of volitional exercise endurance training, since improvements in the GET are normally proportionately greater than those found in $\dot{V}_{O_{2peak}}$ [173, 92, 117]. Nonetheless, an increased capacity for heavy work was found over the first 6 months here: all subjects were able to cycle continuously for 60 min and their P_{peak}^t and $\dot{V}_{O_{2peak}}$ had increased significantly (see chapter 4).

6.5.4 The RC point

The RC point was found to have significantly increased between 3 and 6 months. This, in addition to the lack of change in the GET, is consistent with the improvements normally only found after periods of high intensity (large anaerobic work element) exercise training, where anaerobic buffering capacity is increased. Röcker *et al.* found that short session, intense training delayed the appearance of the RC point only, indicating an increase in the isocapnic buffering phase (GET to RC point), by improving anaerobic buffering capacity [146]. Periods of long session, moderate intensity endurance training (primarily aerobic work) normally increase the work rate at which both the GET and the RC appear as a result of improvements in aerobic capacity [117]. The changes in gas exchange thresholds found in this study are consistent with the changes that are normally elicited by periods of intense anaerobic training.

6.5.5 Lactate production

Indeed, given the degree of anaerobiosis elicited by this form of exercise, the significant reduction in the $\text{La}^-/P_{\text{peak}}^t$ values after 9 months may suggest improvements in La^- transport and H^+ buffering capacity, and oxidative potential [139]. It is interesting that these changes were not apparent after 12 months of training. This could be due to the subjects having reached their peak training frequency by 6 months (see chapter 4) and their highest cycling resistance capacity after about 6–9 months (reported in training diaries). This may also explain why the delay in RC point noted at 6 months was no different to pre-training values after 12 months.

It is not clear why one subject (no. 5) failed to elicit a GET or an RER in excess of one during the any IWRT. At 57 yrs old, this subject was the oldest in the group, but in all other respects, this individual's cardiorespiratory and power responses to stimulation were very similar to the others and his $\text{La}^-/P_{\text{peak}}^t$ values were very similar to the group mean values. It is possible that his muscle fibres had retained a degree of oxidative capacity or that he had a large capacity for CO_2 storage. A histological investigation may help to explain this phenomenon further.

It would appear, therefore, that the absolute or relative GET values attained during FES cycling for individuals with paraplegia give no useful indication of their endurance work capacity. This is because, for most, there is a degree of anaerobiosis from the outset of ES exercise regardless of exercise intensity and training status, therefore, all ES exercise would be regarded as being in the heavy work domain [173]. Knowledge of the RC point, however, appears to give a useful indication of improvements in endurance capacity by changes in isocapnic buffering capacity. Unfortunately, an RC point was not reached during each test for all subjects, possibly due to peripheral limitations and is therefore of limited use.

6.5.6 Threshold intensity exercise prescription

Given the findings here, and considering that individuals normally train at full stimulation charge and at their highest cycling resistance load during training, then the use of gas exchange thresholds for training intensity prescription would appear to have no utility during ES exercise training. It may be more informative to examine continuous pedalling duration and mean exercise \dot{V}_{O_2} during training as indicators of endurance capacity for this type of exercise. An examination of the gas exchange kinetics and the RER responses during exercise may also give more useful indications of changes in aerobic and anaerobic capacity over time for these subjects and with this type of exercise and this is examined in the following chapter.

6.6 Conclusions

The GET, detected in all but one subject during the course of the study, was found at a cardiorespiratory stress equivalent to that normally elicited by very gentle volitional exercise. This appears to be due to the non-physiological recruitment pattern that normally occurs during ES exercise, which causes an unnatural and measurable degree of anaerobiosis from the start of exercise. The GET was not found to have delayed after training, probably due to the continued recruitment of anaerobic muscle fibres from the outset of exercise. Favourable adaptations appear to have occurred in anaerobic buffering capacity and in lactate handling, similar to those normally associated with high intensity anaerobic training. These adaptations had reversed by 12 months when training was no longer progressive. It appears that the use of the gas exchange threshold paradigm in relation to the determination of exercise endurance capacity or for training intensity prescription for ES exercise with the SCI population is invalid. An examination of exercise capacity in terms of exercise duration and the highest and sustained cardiorespiratory responses during ES training may provide more useful indicators of changes in endurance capacity after ES exercise training.

Accordingly, the following chapter will examine the cardiorespiratory responses elicited by a 60 min FES cycle training session in subjects that had trained for 12 months and examine these responses in relation to those elicited by the corresponding IWRT tests.

Chapter 7

A comparison between the cardiorespiratory stresses elicited by stimulated cycle training and testing

...man will occasionally stumble over the truth, but usually manages to pick himself up, walk over or around it, and carry on.

Winston S. Churchill

This chapter briefly outlines the principles underpinning traditional, volitional maximal aerobic capacity tests and questions their use as valid measures of the peak cardiorespiratory stress that can be elicited by FES cycling. This argument was based on comparisons made between the cardiorespiratory responses elicited by a traditional IWRT and those elicited during an FES HTS after a period of 12 months of high-volume training. The respiratory gas exchange dynamics over the course of the HTS were also examined and characterised for the first time during FES cycling. The preliminary outcomes of this study were presented as a poster at an international conference in 2006 and the findings from this study are currently in preparation as a journal article:

H. Berry, C. Perret, K.J. Hunt, S. Grant, B.A. Saunders, D.B. Allan, and T.H. Kakebeeke, "Conventional incremental exercise test protocol underestimates peak oxygen uptake during stimulated cycle ergometry in paraplegia" *11th Annual Congress of the European College of Sport Science, Lausanne, Switzerland, 5-8th July, 2006.*

H.R. Berry, T.H. Kakebeeke, N. Donaldson, D.B. Allan and K.J. Hunt. The peak cardiorespiratory stress elicited by stimulated cycle training and testing. *Medicine*

and science in sports and exercise, in preparation.

7.1 Introduction

\dot{V}_{O_2} is normally regarded as the most important parameter in determining an individual's capacity for and tolerance to exercise since oxidative (aerobic) metabolism is the principal means by which the body generates energy during low to moderate intensity work. Non-oxidative (anaerobic) metabolism supplements the energy supply as exercise becomes more intense, or forms the principal energy source where exercise is performed at very high intensity for short periods [5].

Volitional exercise testing Traditional whole body tests are based on this metabolic paradigm, whereby during an incremental work rate exercise test, \dot{V}_{O_2} will increase linearly with work rate until it reaches or plateaus at its highest level (see chapter 6). Providing that there has been no peripheral limitation to work, this will normally indicate that the cardiorespiratory system has reached its maximum aerobic power or $\dot{V}_{O_{2max}}$. Any increase in work intensity beyond this point, termed supra-maximal, is very limited and will not cause an increase in \dot{V}_{O_2} but is fuelled by anaerobic metabolism and will lead to very rapid fatigue and an early termination of exercise.

Gas exchange kinetics The respiratory gas exchange (Y) response to a change in exercise intensity (the on-transient kinetics) at any time (t) is phasic and exercise intensity dependent: for light to moderate exercise transitions ($< GET$), \dot{V}_{O_2} normally display a bi-phasic response (phase I; cardiodynamic, reflecting an abrupt increase in \dot{V}_{O_2} as a result of increased pulmonary blood flow [28], phase II; primary, reflecting the transient adjustment in oxidative muscle metabolism to meet the increased energy demand). If exercise is continued at a constant work rate, and this is in the heavy exercise domain ($> GET$), an additional phase becomes evident after about 2 min (phase III, the slow component, reflecting a disproportionate, time and work rate dependent, increase in oxygen demand). Exercise intensities beyond $\dot{V}_{O_{2peak}}$ (severe work intensity) display kinetics that are best described by a bi-phasic response only (phases I and II) [132].

Phase I can be best explained by the first part of equation (7.1), where $Y(b1)$ is the value before the step change in exercise, A_c is the asymptotic amplitude for the linear, first order exponential term, which starts at the onset of exercise, or step change in exercise (time (t) = 0), and τ_c is the time constant.

Phase II is described by the additional term indicated in equation (7.1), where the exponential term starts after an independent time delay (TD_p), with a value that corresponds to the end of phase I ($A_c + Y(b1)$), and with the asymptotic amplitude A_p .

The kinetics of phase III are well defined by a further, additional term, as indicated in equation (7.1) where, after a time delay (TD_s), the value at the asymptote of phase II ($A_p + A_c + Y(b1)$) is used as the starting point for the exponential term towards the asymptote A_s . The magnitude of this slow component is dependent on exercise intensity and the time of measurement. It is often quantified as the difference in \dot{V}_{O_2} between the value at the asymptote of phase II and the end of exercise.

$$\begin{aligned}
 Y(t) = & Y(b1) + A_c * \left(1 - e^{-\frac{t}{\tau_c}}\right) \text{ phase I} \\
 & + A_p * \left[1 - e^{-\frac{(t-TD_p)}{\tau_p}}\right] \text{ phase II} \\
 & + A_s * \left[1 - e^{-\frac{(t-TD_s)}{\tau_s}}\right] \text{ phase III}
 \end{aligned} \tag{7.1}$$

\dot{V}_{O_2} will normally have reached a steady state by 3 min for healthy subjects during constant work rate light and moderate intensity exercise. The τ for this phase is inversely proportional to fitness and cardiopulmonary health levels with values for healthy individuals ranging from 20 to 45 s, and up to 90 s in cardiac patients [93]. The slope of the increase in \dot{V}_{O_2} and the τ is also affected by inactivity, age and pathological condition, but unaffected by work rate with a gain of 9 to 11 ml/min/W normally seen [179].

The phase III slow component will either slow or prevent the attainment of \dot{V}_{O_2} steady state during heavy exercise stages. Work intensities beyond the RC point, or *critical power* level (see chapter 6) are regarded as severe and \dot{V}_{O_2} will not reach a steady state, but will increase towards $\dot{V}_{O_{2peak}}$. Providing that exercise is not in the *extreme* domain and limited by peripheral fatigue (exercise duration < 140 s), then the higher the work intensity, the shorter the time to reach $\dot{V}_{O_{2max}}$ at each stage [93].

Electrically stimulated exercise testing Our understanding of the unique motor unit recruitment patterns that occur during surface stimulation (see section 1.3.2) has led us to question the interpretation of cardiorespiratory responses that are elicited by an FES cycling IWRT that has been designed to elicit responses according to the progressive oxidative-glycolytic metabolic paradigm of volitional exercise (see chapter 6).

It appears that during FES cycling there is an unnatural and early, intensity independent, contribution to overall energy production from anaerobic metabolism that does not seem to be altered by training and which results in an O_2 cost of work about 3.5 times that of volitional exercise (chapters 5 and 6). The HTS was performed at a maximally tolerated resistance from the outset and this was adjusted throughout the exercise session, as the muscles fatigued, to enable the subjects to continue pedalling within the given cadence range. The gas exchange response kinetics measured over the first 3 min of the training session will give valuable insights into the oxidative-glycolytic responses to the imposed maximal cycling load. In light

of the study findings from chapters 5 and 6, novel outcome measures were specifically designed to measure these responses during the on-transients of a FES HTS for the first time during FES cycling.

FES exercise testing The IWRTs performed in this study were achieved by gradually increasing the stimulation pulse duration to enable the cadence controlled FES cycling power to increment at a steady rate of either 1 or 2 W per minute until stimulation reached SS point [55]. Cycling power had reached its highest level by this point and was regarded as P_{peak}^t . The protocol required that stimulation was then reduced to allow a period of recovery at the lowest stimulated work rate. However, in some cases (for technical reasons), the stimulation was not immediately reduced to the lowest stimulated work rate. In these instances, it was noted that power often dipped slightly and that \dot{V}_{O_2} often continued to rise during this period of maximum stimulation. Nonetheless, to ensure that valid test to test comparisons were made, the \dot{V}_{O_2} at SS was taken as $\dot{V}_{\text{O}_{2\text{peak}}}$. Accordingly, the true IWRT $\dot{V}_{\text{O}_{2\text{peak}}}$ was not known.

Training sessions After the first 3 months of cycle training, it became apparent that the IWRTs were not providing the same degree of cardiorespiratory stress that was provided during the HTS. Subjective observations were that the HTS were far more intense and more physically exhausting than the IWRTs where it was also found that breathing was heavier, and it was common for individuals to perspire during training, but not during testing.

Accordingly, this chapter determined the training \dot{V}_{O_2} intensity in relation to $\dot{V}_{\text{O}_{2\text{peak}}}$ to examine the validity of the current IWRT for the determination of maximal aerobic performance during FES cycling. The cardiorespiratory responses to prolonged FES cycling sessions of variable resistance and variable cadence were also examined and characterised by examining the dynamic gas exchange responses over the first 3 minutes of exercise and the mean cardiorespiratory stress over the final 57 min of the HTS. The highest and mean cardiopulmonary response values were compared to the peak values that were recorded during the final IWRT tests. The on-transient respiratory exchange was examined using novel measures that were devised here specifically for FES exercise.

7.2 Methods

Please refer to chapter 3 for a full and detailed description of the methods and of the statistical analysis employed in this study. Methods peculiar to this part of the study are given below.

7.2.1 Subjects

8 of the 11 subjects that had completed 12 months of FES cycle training were studied for this investigation. These subjects are detailed in table 7.1

Table 7.1: The Subjects

Subject	Gender	Age	Lesion level	Years since injury	Height (cm)	Body mass (kg)
1	F	35	T7	15	162	64
2	M	43	T9	25	186	67
3	M	40	T4	11	184	70
5	M	57	T4	9	173	85
6	M	44	T4	4	170	76
7	M	39	T3	8.5	177	83
8	M	38	T3	12	183	73
11	M	44	T9	20	175	74
Mean		42.5	5.4	13.1	176.3	74
SD		6.7	2.6	6.8	8.1	7.3

7.2.2 Testing

The equipment used for the HTS is fully detailed in chapter 3. Fig. 7.1 shows one subject being monitored during her final HTS.

During the IWRT, stimulation was increased progressively to SS point over 8–12 min to permit work rate to increment at an isokinetic steady rate of either 1 or 2 W per minute. The exercise was terminated shortly after reaching SS point. Conversely, during the HTS, and after one or two minutes of manually assisted passive cycling (to help minimise the occurrence of muscle spasms at the onset of stimulation), stimulation was applied rapidly to SS point (over about 60 s) with the trainer set at the session HRL. The HRL was chosen to provide a maximal session training stimulus from the outset and to ensure that the muscles were working against sufficient resistance to prevent the cadence from exceeding 50 rpm (for most of the subjects, it was observed that the fresh, maximally stimulated, trained muscles were capable of propelling the legs at cadences well in excess of 50 rpm). Stimulation was then held constant over the remaining exercise period, during which time the trainer resistance and gears were altered in an attempt to keep the cadence within the given range of 35–50 rpm.

Subjects' breath by breath respiratory gas exchange and heart rate were monitored during a HTS (60 min pedalling against HRL to maintain a target cadence of between 35 and 50 rpm) performed shortly after completing 12 months of FES cycle training. Each subjects' cardiorespiratory responses were examined and compared to those elicited by their corresponding 12-month IWRT (as detailed in chapter 3).

7.2.3 Outcome measures

The following outcome measures were determined during the HTS:

$\dot{V}_{O_2\text{high}}$: this was determined as the highest \dot{V}_{O_2} of a 60 second rolling average taken over the exercise phase.

$\dot{V}_{O_2\text{mean}}$: the average \dot{V}_{O_2} taken over the last 57 min of exercise.

HR_{high} : the highest 60 second average heart rate over the exercise phase.

RER_{high} : this was the highest 60 second rolling average value for the RER over the exercise phase.

$\text{T}_{\text{RER}1}$: the time from onset of stimulated exercise to where $\text{RER} = 1$.

RER_{mean} : the average RER taken over the last 57 min of exercise.

$\dot{V}_{O_2} \tau^{0-3}$: the time constant for the increase in \dot{V}_{O_2} over the first 3 min of exercise.

$\text{RER}\tau^{0-3}$: the time constant for the rise in RER over the first 3 min of exercise.

For \dot{V}_{O_2} or RER (Y) at any given time (t), the transition phase over the first 3 min of exercise was best described by the mono-exponential term, as given for phase I in equation (7.1). The RER appeared to display a mono-exponential response after recovery from the expected slight dip immediately following exercise onset. $Y(b1)$ is the pre-exercise value, A_c is the amplitude for the exponential term at 3 min following start of exercise. The exponential term started at the onset of exercise (\dot{V}_{O_2}) or after values had regained their pre-exercise values (RER) ($(t) = 0$), and τ_c is the time constant. The gain was not able to be calculated, since the training work rate in Watts was not known.

7.3 Results

Full data sets ($N = 8$) were available for all but one subject (due to technical difficulties, only heart rate and \dot{V}_{O_2} data were available for subject no. 11). A summary of outcomes are given in table 7.2. Changes in pedalling cadence during the HTSs are shown in Figs 7.3(b) and 7.4(b).

7.3.1 Cardiorespiratory responses

Oxygen uptake There was a significant difference between the IWRT $\dot{V}_{O_2\text{peak}}$ and the HTS $\dot{V}_{O_2\text{high}}$ (a difference of 149 ± 78 mL/min, $P = 0.001$). The $\dot{V}_{O_2\text{mean}}$, sustained over 57 min of FES cycling was not significantly different from the IWRT $\dot{V}_{O_2\text{peak}}$ value (a difference of 4 ± 34 mL/min, $P = 0.75$) (Table 7.2). Fig. 7.2 shows a comparison between the \dot{V}_{O_2}



Figure 7.1: Monitoring cardiorespiratory responses during a FES cycle training session for one subject in their home.

Table 7.2: Final training session and incremental work rate test outcome measures

Variable	mean	SD	Min	Max
HTS				
$\dot{V}_{O_2\text{high}}$ (mL/min)	915	289	537	1381
$\dot{V}_{O_2\text{mean}}$ (mL/min)	762	253	431	1157
HR_{high} (beats/min)	111	25	79	150
RER_{high}	1.39	0.16	1.13	1.58
T_{RER1} (s)	78	10	64	91
RER_{mean}	1.01	0.05	0.93	1.09
$\dot{V}_{O_2} \tau^{0-3}$ (s)	32	9	20	45
$RER\tau^{0-3}$ (s)	61	46	28	160
IWRT				
$\dot{V}_{O_2\text{peak}}$ (mL/min)	766	240	447	1147
HR_{peak} (beats/min)	92	19	69	115
RER_{peak}	1.15	0.11	0.96	1.28

HTS, home training session; IWRT, incremental work rate test; $\dot{V}_{O_2\text{high}}$, the highest 60 s average oxygen uptake value; $\dot{V}_{O_2\text{mean}}$, the mean \dot{V}_{O_2} over the last 57 min of exercise; HR_{high} , the highest 60 s average heart rate; RER_{high} , the highest 60 s average RER; RER_{mean} , the mean RER over the last 57 min of exercise; $\dot{V}_{O_2} \tau^{0-3}$ and $RER\tau^{0-3}$ \dot{V}_{O_2} , time constants over the first 3 min of exercise.

responses measured during the IWRT (black dots) and final HTS (blue dots). Here it can be seen that the HTS \dot{V}_{O_2} reached a level very similar to the IWRT $\dot{V}_{O_2\text{peak}}$ very early on during the training session and continued to rise throughout, despite changes in training resistance.

Heart rate The HR_{high} recorded during the HTS was significantly higher than the IWRT HR_{peak} value (a difference of 21 ± 9 beats/min, $P = 0.001$) (Table 7.2).

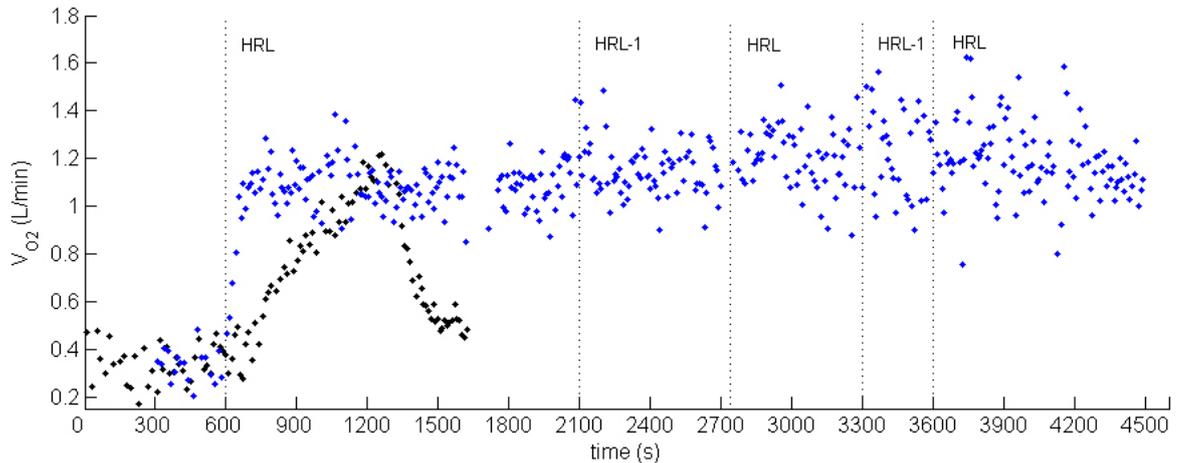


Figure 7.2: A comparison between the \dot{V}_{O_2} response (a 9 breath average is shown for clarity) during a home training session (blue dots) and the associated IWRT (black dots) for one subject after 12 months of training. The trainer resistance was set at the HRL at the start of training (600 s). The subject removed his mask at 1620 s to take a drink. Resistance was reduced (HRL-1) and restored (HRL) where indicated by the dotted vertical lines.

RER The HTS RER_{high} was significantly higher than the IWRT RER_{peak} by 0.24 ± 0.12 , $P = 0.002$ and the HTS RER_{mean} was significantly lower than the IWRT RER_{peak} (a difference of 0.14 ± 0.09 , $P = 0.006$) (Table 7.2).

7.3.2 0-3 on transient kinetic response

Oxygen uptake The \dot{V}_{O_2} rose rapidly during the first three minutes, reaching an asymptote within this time. The \dot{V}_{O_2} τ^{0-3} of 32.4 ± 9 s had a range of 20–45 s across individuals. The rapid rise in \dot{V}_{O_2} can be seen clearly in Figs 7.2, 7.3(a) and 7.4(a).

Metabolic gas exchange The RER rose sharply in each case and reached unity within only 64–91 s with a $RER\tau^{0-3}$ of 61 ± 46 s. This can be seen in Figs 7.3(a) and 7.4(a) and detailed in Table 7.2. Data sets were examined for evidence of a hyperventilation in relation to \dot{V}_{CO_2} during the rise and peak of RER and none was found for any of the training sessions.

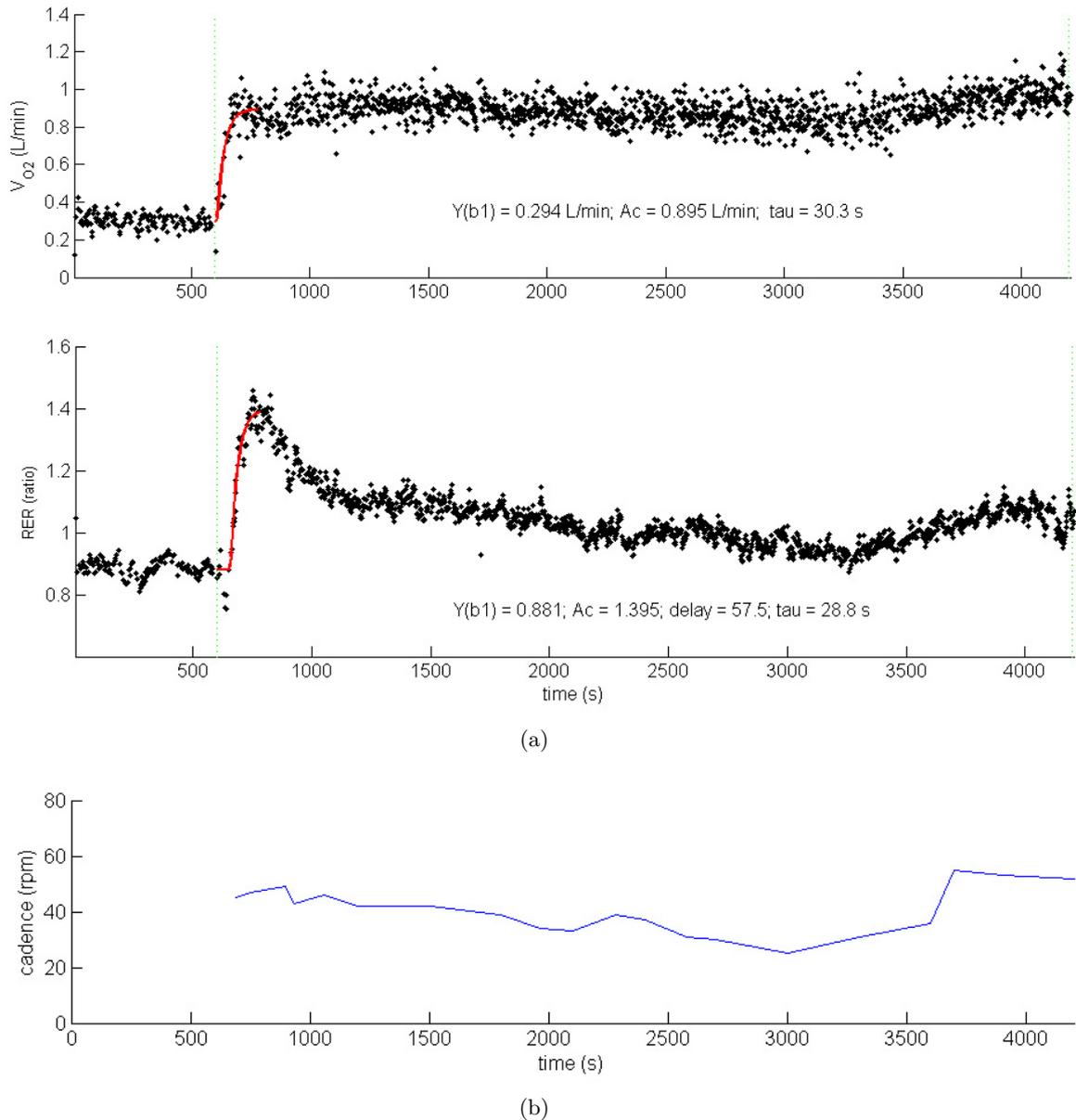


Figure 7.3: (a) Plots show the representative on-transient kinetic response curves (red) for subject no. 7, fitted to raw breath by breath data from the onset of FES cycling during a home training session (HTS). The top panel shows a curve fitted to the \dot{V}_{O_2} response and the lower panel shows the RER response curve, fitted after the initial dip and recovery to pre-exercise value (delay). $Y(b1)$ represents the pre-exercise value, A_c is the value after 3 min of exercise and τ is the time constant. Plot (b) shows the variations in pedalling cadence over the exercise session. The session was conducted at a constant trainer resistance, but the gears were changed to adjust pedalling resistance in an attempt to maintain a cadence of between 35 and 50 rpm.

7.4 Discussion

7.4.1 Cardiorespiratory stress

This study set out to compare the highest and mean cardiopulmonary responses measured during an FES cycling HTS after 12 months of training to the peak values that were recorded

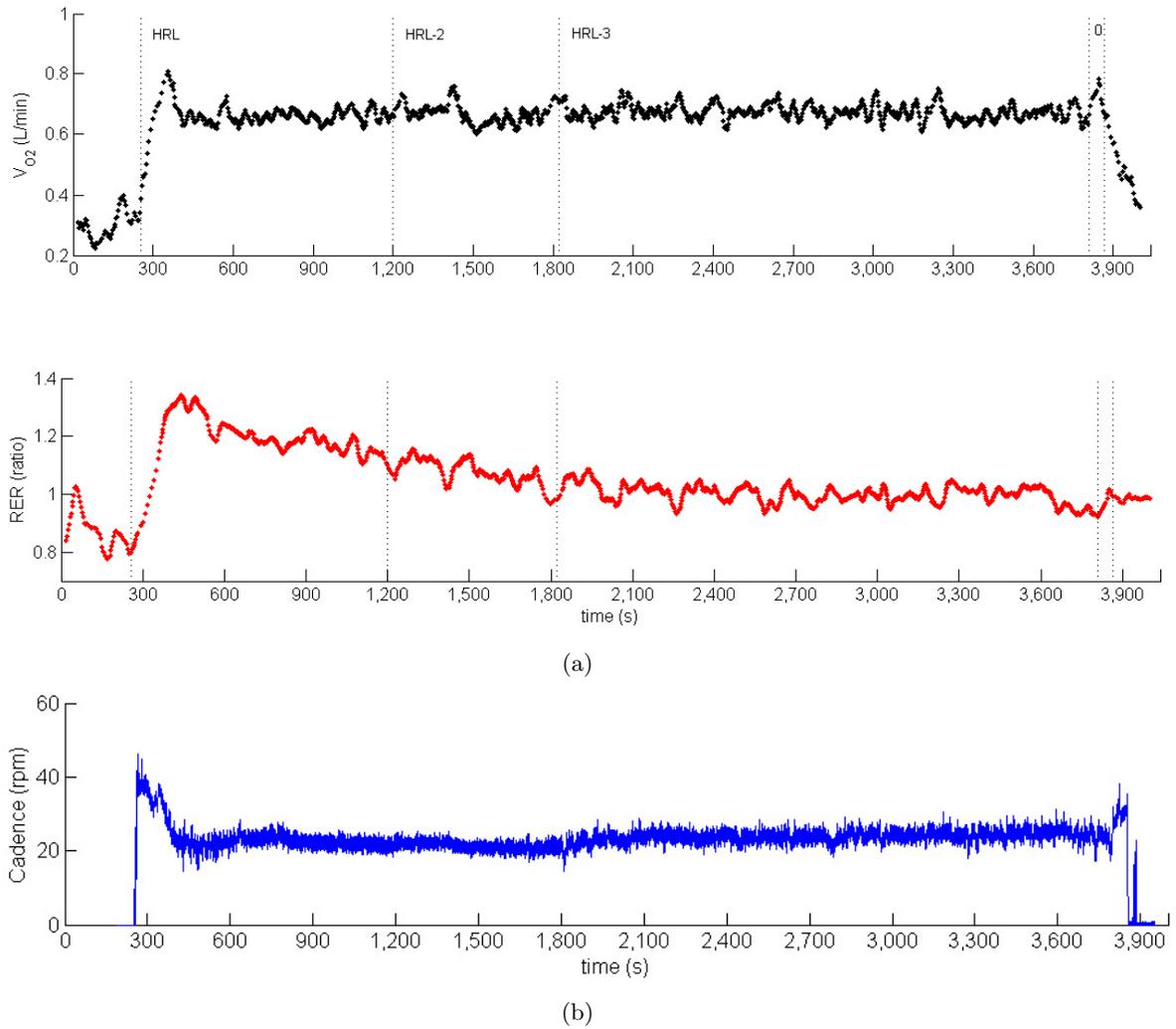


Figure 7.4: Plot (a) shows the breath by breath gas exchange data for subject no. 2 during his final HTS (9 breath averages are shown for clarity). The top panel shows the \dot{V}_{O_2} response and the bottom panel shows the RER response over the training session. The first dotted vertical line indicate the start of cycling at the HRL. Subsequent dotted lines indicate subsequent reductions in trainer resistance level (HRL-n). 0 indicates that all trainer resistance was removed. Plot (b) shows the cadence trace for each pedal rotation throughout the exercise. This subject was unable to pedal at a cadence of 50 rpm, but found that his legs were able to pedal for extended periods at about 25 rpm with a peak of about 40 rpm.

during an IWRT test. The cardiorespiratory responses to the HTSs of variable resistance and variable cadence were also examined and characterised by examining the dynamic gas exchange responses over the first 3 minutes of exercise and the mean cardiorespiratory stress over the final 57 min of the HTS. The on-transient respiratory exchange response was also examined for the first time using novel measures that were devised specifically for FES exercise.

Here it was found that the HTSs were found to elicit a significantly higher cardiorespiratory stress than that recorded during the associated IWRTs. For the HTS, the $\dot{V}_{O_2\text{high}}$,

HR_{high} and RER_{high} were 20%, 29% and 21% higher, respectively, than the associated IWRT peak values for each variable. Additionally, the $\dot{V}_{O_2\text{mean}}$, sustained over the last 57 min of FES exercise was not significantly different to the $\dot{V}_{O_2\text{peak}}$ recorded during the IWRTs. The reasons for this appear to be due to differences in the rate of stimulation and pedalling resistance application, cadence and to the duration of maximally stimulated work for each exercise.

Because of the disordered, synchronous motor unit recruitment pattern found during ES, and the type II fibre type predominance after SCI, the total systemic \dot{V}_{O_2} will comprise of the cost of muscle activation and relaxation, the cost of ATP replenishment in the FG and FOG fibres, lactate transport and oxidation for re-use, lactate conversion to glycogen in the liver (cori cycle), and the oxygen cost of trans-membrane ion pumping. The additional oxygen cost associated with any unrelated muscular activity, the increase in ventilatory work and of maintaining systemic homeostasis will also be included [173]. These factors are thought to cause the time and work rate dependent reduction in efficiency (the \dot{V}_{O_2} slow component) normally seen during volitional exercise in the heavy work domain [93]. Here, the anaerobic contribution to work over the course of the 60 min training session will have produced a \dot{V}_{O_2} slow component and this may explain why the \dot{V}_{O_2} intensity level was sustained and sometimes even increased, even when the trainer resistance level was reduced (Figs. 7.2 and 7.4).

Accordingly, the \dot{V}_{O_2} during FES cycling would be expected to continue to rise beyond SS point until fibre fatigue and recovery rates had reached an equilibrium level and the cost of maintaining systemic homeostasis had reached its peak. This was not observed during the IWRTs, because tests were terminated before \dot{V}_{O_2} had reached a peak value.

7.4.2 On-transient gas exchange

A curve was fitted to the first three minutes of the on-transient \dot{V}_{O_2} and RER response to the HTS for each subject. From this it was clear that a maximal muscular metabolic stress was elicited from the outset, that caused the \dot{V}_{O_2} and the RER to rise rapidly towards an asymptote, which for the \dot{V}_{O_2} , was often near or at the $\dot{V}_{O_2\text{high}}$ value, with a τ^{0-3} of only 20 to 45 s. This range in values is no different to that expected in healthy able bodied individuals performing volitional exercise and would suggest that there was no apparent limitation in the central or peripheral response to the increase in metabolic demand. The very rapid rise in the RER to reach 1 within only 60–90 s with a τ^{0-3} of between 28 and 160 indicates the recruitment of a high proportion of type II fibres from the outset. This also provides strong metabolic evidence for a disordered motor unit recruitment which caused a substantial anaerobic contribution to work from the outset of ES exercise [69].

In the only other study to examine the respiratory responses to prolonged FES cycling [161], the RER was also observed to rise to a very similar peak of ~ 1.3 , but RER did not

reach 1 until after about 5 min of exercise. However, since stimulation was ramped up to SS point over the first 5 min, the relative rate of rise in RER in relation to the rise in SS was almost identical to that found here.

Theisen *et al.* [161] did not observe such a rapid rise in \dot{V}_{O_2} in their study. Instead, they observed an steady rise in \dot{V}_{O_2} response as stimulation increased to SS point over the first 5 minutes. During this time, power output rose rapidly to its peak value, before falling and then recovering again to a lower, sustainable level. It appears that the main difference between these two studies is that the variable power study did not impose a load on the leg muscles, whereas, a maximal tolerated load was imposed on the leg muscles from the start of the HTS. This meant that the power produced at the onset of work here was an indistinguishable combination of peak anaerobic and aerobic power output. Whereas, during the variable power study, peak anaerobic and peak aerobic power output were most likely produced sequentially, as fibres fatigued and then recovered and were distinguishable by time, in response to the gradual increase in stimulation and recruitment of motor units.

Interestingly, the swift application of maximal tolerated cycling load during the HTS is not dissimilar to that applied at the outset of short-lasting maximum effort exercise [50] or an ‘all out’ maximal intensity volitional cycling test (severe or extreme work intensity), such as the Wingate Anaerobic Test [178]. These tests are designed to test maximum anaerobic power capacity over only 30 s, and are normally terminated before the aerobic system has had enough time to reach its maximum capacity.

In an attempt to find out whether \dot{V}_{O_2} could be increased to $\dot{V}_{O_{2max}}$ during this type of test, two studies looked at the \dot{V}_{O_2} responses during longer maximal tests of 90 s in duration, and it was found that this was long enough to elicit a maximal \dot{V}_{O_2} response in a group of teenage boys and girls [177] and in a group of teenage boys, but not in middle aged men [27]. This was attributed to the significantly faster \dot{V}_{O_2} kinetics observed in the group of boys. More recent, similar tests of 180 s duration have concluded that although it is possible to achieve $\dot{V}_{O_{2peak}}$ during such tests, it is by no means certain, probably due to inter-individual differences in \dot{V}_{O_2} dynamics and peripheral fatigability [25, 166].

The important difference between these short, all out tests, and the HTS sessions is that the subjects on this study were, quite uniquely, able to produce a maximal muscular *effort* from the outset and maintain this *all out* effort, albeit of diminishing power, beyond the initial rapid fatigue phase and for the entire 60 min exercise session.

Maximum voluntary muscular efforts cannot normally be sustained for more than a couple of minutes before contractile function is affected: Ca^{2+} handling becomes slower and muscle relaxation times increase. Additionally, the excitability of the muscle membrane reduces as K^+ build up in the extracellular space [94]. The associated neurological feed back from peripheral chemoreception and nociception that would normally influence ‘willpower’, and provide a central limitation to maximal exercise performance, is not present after SCI. It

appears, therefore, that FES cycling can continue for as long as the continuously stimulated muscle fibres are physically able to contract and relax and produce sufficient power to overcome the resistance at the pedals.

It is possible that the rapid application of stimulation during the HTS may have caused stretch reflex contractions to occur in antagonistic muscle groups. This would increase overall metabolic demand but reduce the ability of the legs to pedal against the HRL, causing the \dot{V}_{O_2} to increase rapidly during this time. Nonetheless, there appeared to be little or no evidence of this since pedalling cadence appeared smooth and was not observed to slow during this time. This phenomenon could also explain the slight drop in power often observed at SS point during the IWRTs. However, the drop in power could also be adequately explained by fibre fatigue in the last fibres to be stimulated, since no further fresh fast, high power motor units were recruitable to increase or maintain this power output.

The higher HR observed during the HTSs is possibly due to a time dependent cardiovascular drift, where reduced plasma volume¹ caused a decrease in stroke volume and a concomitant increase in heart rate, disproportionate to \dot{V}_{O_2} , to preserve cardiac output [115].

Hooker *et al.* [79] attributed the reductions in RER that were observed over an isokinetic, 30 min FES cycling exercise to substrate depletion. However, in this study, RER_{mean} was between 0.93 to 1.09, with values often seen to increase to beyond unity near the end of the session as cadence increased as a result of changes in gearing, or as trainer resistance was removed (see Figs. 7.3 and 7.4). These observed increases in RER after 60 min of cycling are quite remarkable and would not be possible where there was a significant degree of glycogen depletion.

7.5 Conclusions

It has been clearly demonstrated that the current IWRT is not a valid test for establishing $\dot{V}_{O_{2\text{peak}}}$ during FES cycling, since the \dot{V}_{O_2} value at SS point was 20% lower than the $\dot{V}_{O_{2\text{high}}}$ attained during prolonged constant stimulation FES cycling. It may be more appropriate to conduct tests that extend beyond SS point, with longer durations at each power level. Discontinuous, short duration incremental tests, conducted at higher pedalling cadences may also elicit higher \dot{V}_{O_2} values and be more appropriate for this subject group and this very unique exercise modality.

The on-transient kinetic gas exchange responses to FES cycling showed no apparent peripheral or central limitation in response. The novel measures used here, T_{RER1} and the $RER\tau^{0-3}$ gave a valuable insight into the on-transient kinetics of the oxidative-glycolytic response to electrically induced maximal exercise for the first time. These measures indicated

¹After about 15 to 20 min of prolonged constant work rate exercise in a thermoneutral environment, central blood plasma volume becomes reduced as a result of the gradual redistribution to the periphery for cooling, a fluid shift from plasma to body tissues and a progressive fluid loss through sweating [115].

the absolute and relative rate of rise in non-metabolic CO_2 production from the start of ES exercise and provide strong metabolic evidence of a disordered, non-physiologic motor unit recruitment pattern. The observed \dot{V}_{O_2} and RER dynamics over the entire exercise session provide strong metabolic evidence for the continual recruitment and recovery of glycolytic fibres throughout.

The remarkable ability of the paralysed, trained and predominantly FOG muscles to produce ‘maximal’ exercise in the equivalent of the heavy or severe muscular work domain during prolonged periods of FES cycling is unique and displays an extraordinary capacity for fibre recovery and anaerobic power capacity. This is likely to explain the unique gas exchange dynamics observed in this study. These outcomes provide compelling evidence to support the design of effective ES exercise training programmes in the future and to inform valid test protocol design for this type of exercise.

Chapter 8

Conclusions

This multi-centre study has clearly demonstrated that regular home-based FES cycle training can provide a cardiorespiratory and musculoskeletal stress that is sufficient to minimise the health risks of inactivity, and significantly increase the health and physical fitness of individuals with complete lower limb paralysis. The upper limits in load tolerance were met by most subjects after 6 months of training, and by all subjects by 9 months during this programme. It is not known whether this was due to a physiological limitation within the stimulated muscles, or to limitations within the current stimulation strategy or the training protocol. Nonetheless, the robust relationship that was found during the progressive training period between training hours completed and improvements in P_{peak}^t and $\dot{V}_{\text{O}_2\text{peak}}$, provide a unique and sound framework with which to guide and compare all future FES cycle training programmes. The conclusions reached here are based upon the thorough, methodical, consistent and systematic data acquisition, treatment and analysis that were performed during this study. The relevance of these findings lie in the strong evidence base that this study provides that can guide future FES cycling prescription and contribute towards the widespread clinical uptake of FES cycling for the health and wellbeing of SCI individuals.

Important contributions have been made here toward the knowledge and understanding of the physiology of ES exercise and to the acute and trained metabolic responses elicited by prolonged, high intensity FES cycle training. The aerobic and anaerobic gas exchange threshold analyses that were performed here provide metabolic evidence in support of the non-physiological, disordered motor recruitment observed to occur during ES exercise. The training session on-transient kinetic gas exchange responses revealed no apparent peripheral or central limitation in meeting the relatively high FES energy demands of the HTS. The novel measures used here, T_{RER1} and the $\text{RER}\tau^{0-3}$ gave unique and valuable insights into, what appears to be, a very rapid oxidative-glycolytic response to electrically induced exercise after 12 months of intensive FES cycle training. These findings, in combination with the respiratory gas exchange threshold observations, the dynamic and steady state oxygen cost of cycling, the blood La^- levels, and the RER dynamics observed during the CWRTs provide

a strong, unequivocal body of metabolic evidence in support of the immediate and continual recruitment and training of fast anaerobic muscle fibres throughout an FES cycling session. These observations highlights the uniqueness of the ES exercise response, and stress the need for new training and testing methods and protocols, tailored specifically to this mode of exercise.

A training-induced increase in aerobic capacity was observed over the course of the training programme, evidenced by the increase in $\dot{V}_{O_{2peak}}$ and in continuous pedalling power and endurance capacity over time. However, the most remarkable and unique observation made here was of the high oxidative-glycolytic endurance capacity that was demonstrated in this FES cycle training. In the few tests where an RC point was detected, it was found to have delayed after 6 months of training, supporting the evidence gathered during the CWRTs that lactate handling and anaerobic buffering capacity had improved during this time. These adaptations have hitherto only been observed after periods of volitional, short-duration, high-intensity anaerobic cycle training. Here, they appear to have permitted the trained paralytic FOG muscle to contract repeatedly and over prolonged periods with a high degree of fatigue resistance, and demonstrated a very high capacity for sustained glycolysis and fibre activation and recovery in the predominantly redundant, paralytic muscle.

These findings would suggest that, for this particular population and exercise modality, the use of GET analysis in determining exercise endurance capacity, or for training intensity prescription purposes, is invalid. The RC point was not often observed and its analysis is not likely to give any more information than can be gained from observing cycling endurance capacity, and the highest and sustained cardiorespiratory responses during FES training.

Although the current IWRT enabled precise respiratory gas exchange thresholds to be performed for the first time in ES exercise, comparisons between the cardiorespiratory stresses of the final HTSs and IWRTs clearly demonstrated that the IWRT is not a valid test for establishing $\dot{V}_{O_{2peak}}$ during FES cycling. Given that the anaerobic contribution to FES exercise is likely to lead to the development of a time and intensity dependent slow aerobic component, even at very low work intensities, it would seem more pertinent to conduct tests that extend beyond SS point to allow this to develop. Accordingly, continuous or discontinuous $\dot{V}_{O_{2peak}}$ tests that consist of longer cycling durations at each power level are likely to elicit higher \dot{V}_{O_2} values than the current test protocol and may be more appropriate for this subject group and this very unique exercise modality.

This was the first study to measure and quantify the electrical and metabolic costs of ES exercise and observe the effects of training on these parameters. These findings here suggest that the electrical cost of work was determined primarily by changes in motor unit size and secondarily by the level of tissue impedance caused by the subcutaneous fat layer. Individual changes in the metabolic cost of FES cycling after 6 months of training was strongly related to changes in the electrical cost of work, suggesting that for this study, FES cycling efficiency

was determined by the quantity of muscle mass activated per unit of power produced, rather than to differences in the metabolic efficiency of the muscle mass itself. These findings suggest that stimulation strategies that are able to target agonist and synergistic muscle groups with more precision may improve the efficiency of this type of exercise.

Notwithstanding the social and psychological benefits that are often gained from engaging in regular physical activity, the physiological benefits gained by the SCI individuals on this FES cycle training study have been clearly demonstrated. The outcomes of this study provide a compelling body of evidence with which to support the increased clinical uptake of FES cycling prescription and to inform the future design of specific, effective, ES exercise training programmes. Further investigations are merited to design, test and validate peak FES cycling capacity test protocols, based on the unique metabolic characteristics of ES exercise that have been identified here. Given the mobility and recreational possibilities of this form of exercise, future work should also be aimed towards determining the optimal combination of stimulation and loading strategies, and training protocols to maximise favourable training responses within a more feasible, lower volume, home-based training programme for this particular population.

Chapter 9

Future work

Life is not merely to be alive, but to be well.

Marcus Valerius Martial

The CNS has demonstrated a capacity for neural plasticity that has the potential to enable some recovery following spinal cord injury. Human and animal studies have both shown physical exercise interventions to be effective in mediating these adaptations [8].

9.1 Exercise and neural plasticity

The effects of voluntary exercise During the 1990s, it was discovered from animal studies that voluntary exercise increased cell proliferation, synaptic plasticity and neurogenesis in the brain along with improvements in learning and mood [164, 34]. These improvements were found to be due to an exercise induced release of a number of neurotrophic factors by the nerve cells in response to voluntary physical activity.

Neurotrophins These proteins protect the nerve cells and promote survival by causing them to grow, multiply and form new dendritic sprouts. One protein in particular, brain-derived neurotrophic factor or BDNF, was found to enhance learning, protect against cognitive decline and improve mood state [33].

Mechanisms responsible Gómez-Pinilla *et al.* set out to investigate the potential mechanisms by which exercise induced this neurotrophin mediated, neuronal plasticity in the CNS of rats [66]. They found that after voluntary wheel running for 3–7 days, BDNF, its receptor, response cascade proteins and growth-related proteins were all increased in the lumbar spinal cord and *soleus* muscles. By comparing control animals to sedentary and exercised animals that had temporary, unilateral paralysis of the *soleus* muscle, they found that basal levels of neuromuscular activity were required to maintain normal levels of BDNF in the neuromuscular system.

Further to this, in a similar study involving spinal cord isolation from supraspinal (descending) and peripheral (ascending) input, but retaining neuromuscular connectivity [65], it was concluded that the level of supraspinal and peripheral input determined the modulation of levels of BDNF in the spinal cord. In 2003, Vaynman *et al.* observed that the BDNF response cascade appears to operate via an exercise controlled positive feedback loop enhancing its own transcription and that of other proteins responsible for neural transmission and plasticity [167].

9.2 Neural recovery after injury

Ying *et al.* (2005) investigated the potential for voluntary exercise induced BDNF and its associated factors to promote the recovery of locomotion in rats after partial spinal cord injury. They found a wheel running dose-dependant increase in levels of BDNF, which compensated for and indeed improved on the losses of this factor that had occurred after hemisection. Associated effectors for the action of BDNF were also higher than sedentary hemisectioned rats and similar to control rats after 28 days of exercise. The findings would suggest that the synaptic pathways under the control of exercise induced BDNF production may have a role in facilitating recovery after spinal cord injury [181].

Electrical stimulation An earlier study [58] with rats showed that increased, voluntary, daily physical activity performed within the restrictions imposed by a lesion induced neuromuscular deficit, was insufficient to produce any evidence of motoneurone sprouting in the paralysed muscle. In contrast to this, when partial denervation was performed after periods of intensive and prolonged daily activity and then the remaining intact neurones were electrically stimulated for only one hour immediately following lesion, evidence of enhanced motoneurone sprouting was found. It is unclear, however, whether this pointed to an enhancement of neurotrophic factor production as a result of prior exercise, or whether the effects of electrical stimulation per se were sufficient to cause this response.

FES potentiation of voluntary movement In an attempt to understand the ‘carry-over’ affect in muscle activity sometimes observed in partially paralysed limbs after periods of functional electrical stimulation (FES), Rushton (2003) [149] hypothesised that it was due to the unique motor neurone firing pattern of FES and the plasticity of nerve synapses. During transcutaneous electrical stimulation of the lower motor neurone, impulses travel along the axon in both directions, causing an unnatural antidromic ‘backfiring’ of impulses to the cell body. Rushton suggested that a plasticity, or strengthening of the upper and lower motor neurone synapse would occur according to Hebb’s postulate; Hebb suggested that the more successful a presynaptic impulse was in generating a postsynaptic action potential, then the stronger that synapse would become. The residual innervation following stroke or

partial upper motor neurone lesion is often insufficient to depolarise the motor axon hillock to threshold level and would therefore lead to a weakening of the synapse.

During FES, the cell body of the motor neurone becomes depolarised by the repeated ‘backfiring’ of the motor neurone, permitting any weak residual presynaptic impulses to reach threshold level more readily, resulting in a degree of restored voluntary movement.

9.3 Stem cell research

In order to achieve functional CNS axonal growth and regeneration after lesion, some form of cell transplant or peripheral nerve graft will be required to provide the axons with a framework for growth since there is usually a loss of neural tissue at the site of lesion [148]. Neural stem cell research has shown limited success in the capacity for embryonic and adult brain neural stem cell transplants to remyelinate damaged neurones [26] and for immature astrocytes to stimulate axon regeneration.

Autologous transplants Olfactory system glial cells circumvent the ethical issues that accompany the use of embryonic or fetal tissues and provide a promising autologous transplant-mediated repair source that avoids the need for immunosuppression; olfactory ensheathing cells (OECs) are capable of remyelinating demyelinated axons and promoting the restoration of function after injury.

However, although OEC transplantation causes axons to regenerate they do not cross the lesion or form post-synaptic connections to any great extent. Functional recovery is most likely to be due to the neuroprotection and sprouting from the intact axons [9]. The harvest of OECs is a highly invasive procedure, therefore, researchers are now investigating the use of readily accessible, olfactory epithelium (OE) cells which have a unique regenerative capacity and have been found to generate populations of active neural progenitors [110].

BDNF and stem cells Deumens *et al.* (2006) found that adding BDNF to a stem cell culture caused a dose-dependent enhancement of neurite outgrowth on immature astrocytes and concluded that multi-factorial strategies should be adopted for stem cell transplantation [46].

9.4 Future research Areas

In a recent review, Vaynman & Gómez-Pinilla (2005) [168] concluded that since exercise has been found to impact on the molecular systems relating to the maintenance of neural function, plasticity and repair, then exercise may be a powerful protective agent pre-injury and as a tool for neural recovery after spinal cord injury, and may facilitate stem cell transplantation therapies.

9.4.1 Improvements in volitional function after partial SCI

FES exercise may be an especially important form of exercise for complete and partial lesion SCI individuals, especially where a high level of physical deconditioning has taken already taken place. Notwithstanding the increasing body of evidence, added to by this thesis, that FES exercise can significantly impact the cardiorespiratory, cardiovascular and musculoskeletal health of individuals with paraplegia and tetraplegia [90], the evidence of an FES mediated potentiation and restoration of voluntary movement in humans, and of motor neurone sprouting after periods of FES in animal studies merits further investigation.

The judicious use of FES exercise soon after SCI may help to maintain or increase the resting levels of BDNF in the CNS and the peripheral nerves. Aside from the possible mood enhancing benefits of exercise enhanced neurotrophin production, the FES induced potentiation of any residual voluntary movement and the neurotrophic effects of BDNF may provide a favourable molecular environment in which positive neurological adaptations can occur, especially where any transplant therapies are being considered. Additionally, for those individuals with a partial lesion or other chronic neurological deficit, any FES induced improvements in residual function may improve quality of life by enhancing existing voluntary motor control, sensation and autonomic responses, improving the efficacy with which ADLs are carried out.

9.4.2 Optimisation of FES stimulation parameters and muscle recruitment patterns

It is important that new FES cycling stimulation strategies are developed that can improve mechanical effectiveness and increase cycling power and efficiency. Strategies could be developed to account for time and intensity dependent changes in muscle fatigue, which influences optimal muscle group contraction frequencies (pedalling cadence). During volitional exercise, force modulation can be achieved beyond the upper limits of motor unit recruitment by varying the activation frequency (rate coding) [94]. The effect of this will depend on the force-frequency relationship of the fibre type employed and on the gradation of force required. If stimulation strategies can be designed to control power in a more natural way, by a combination of changes in contraction frequency, motor unit activation and in rate coding (stimulation frequency), then we may have a more effective and efficient stimulation paradigm that can lead to greater improvements in FES cycling power production.

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