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ABDOMINAL FUNCTIONAL ELECTRICAL
STIMULATION TO IMPROVE RESPIRATORY
FUNCTION IN ACUTE AND SUB-ACUTE
TETRAPLEGIA

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Abstract

An injury to the cervical region of the spinal cord can cause paralysis affecting all four limbs, termed tetraplegia. People with tetraplegia also have paralysis or impaired function of the major respiratory muscles, namely the diaphragm and intercostal and abdominal muscles. This often reduces respiratory function, with associated respiratory complications a leading cause of morbidity and mortality for this population. Abdominal Functional Electrical Stimulation (AFES), the application of electrical pulses to the abdominal muscles causing them to contract, has been shown to improve respiratory function in tetraplegia. Despite these positive results, further work is needed to establish AFES as a standard clinical treatment. The aim of this thesis is to support the clinical introduction of AFES. This was achieved by addressing two primary objectives. Firstly, the development of new technologies and protocols to optimise AFES for use in a clinical setting. Secondly, the clinical evaluation of these technologies and protocols with tetraplegic patients.

For research purposes, AFES has typically been applied manually, requiring an operator to synchronise stimulation with respiratory activity. One important step necessary for the clinical introduction of AFES is the development of an automated AFES device that can apply stimulation in synchrony with the users respiratory activity, with different stimulation parameters applied for different breath types such as a quiet breath and a cough. In this thesis, the signal from a non-intrusive respiratory effort belt, worn around the chest, was used to develop a statistical classification algorithm capable of classifying respiratory activity in real-time, and applying AFES in synchrony with the user's respiratory activity. The effectiveness of AFES can also be enhanced by stimulating at the abdominal muscle motor points. In this thesis the positions of the abdominal motor points were located systematically for the first time, in ten able bodied and five tetraplegic participants.

To aid the clinical introduction of AFES it is necessary to establish the patient groups who would benefit most from this intervention, and to develop appropriate clinical protocols. This is addressed in two clinical studies, where the feasibility and effectiveness of AFES to improve the respiratory function of the acute ventilator dependant and sub-acute tetraplegic populations was demonstrated. In the first study, conducted with 10 acute ventilator dependant tetraplegics, AFES was applied on alternate weeks for a total duration of eight weeks. This resulted in acute improvements in breathing and led to a longitudinal increase

in respiratory function over the study duration. It was found that participants weaned from mechanical ventilation on average 11 days faster than matched historic controls.

Previous work, which investigated the effect of a three week AFES training programme on the respiratory function of people with sub-acute tetraplegia, suggested that an extended AFES training programme may be more effective. In the second clinical study in this thesis, a continuous eight week AFES training protocol (combined with a six week control period) was evaluated with three sub-acute tetraplegic participants. The application of AFES led to an acute increase in respiratory function, with a longitudinal improvement in respiratory function observed throughout the study. In a single participant case study, the feasibility of combining AFES with assisted coughing delivered by mechanical insufflation-exsufflation was demonstrated for the first time. This was shown to lead to an acute improvement in respiratory function at six of the eight assessment sessions, indicating that this technique could be used to aid secretion removal.

This thesis highlights the feasibility and effectiveness of AFES to improve the respiratory function of the acute ventilator dependant and sub-acute tetraplegic populations. The clinical protocols that enable AFES to be used with these patient groups, and the technological developments detailed throughout this thesis, are an important step towards the introduction of AFES as a regular treatment modality.

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“We must not forget that when radium was discovered no one knew that it would prove useful in hospitals. The work was one of pure science. And this is a proof that scientific work must not be considered from the point of view of the direct usefulness of it. It must be done for itself, for the beauty of science, and then there is always the chance that a scientific discovery may become like the radium a benefit for humanity.” Marie Curie

Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, that this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

All of the analysis and data collection techniques presented in this thesis were created by the author.

E.J. McCaughey

August 2014

Abbreviations

SCI: Spinal cord injury

FES: Functional electrical stimulation

AFES: Abdominal functional electrical stimulation

QENSIU: Queen Elizabeth National Spinal Injuries Unit

RTAs: Road traffic accidents

ASIA: American Spinal Injuries Association

AIS: ASIA impairment scale

UMN: Upper motor neuron

LMN: Lower motor neuron

V_T : Tidal volume

V_T/kg : Weight corrected tidal volume

CPF: Cough peak flow

MEP: Maximum expiratory pressure

MIP: Maximum inspiratory pressure

V_C : Vital capacity

FVC: Forced vital capacity

FVC/kg : Weight corrected forced vital capacity

V_C/kg : Weight corrected vital capacity

ATS: American Thoracic Society

ERS: European Respiratory Society

FEV_1 : Forced exhaled volume in one second

NMES: Neuromuscular electrical stimulation

TENS: Transcutaneous electrical nerve stimulation

IMV: Intermittent mandatory ventilation

SBT: Spontaneous breathing trial

MI-E: Mechanical insufflation-exsufflation

RMT: Respiratory muscle training

PNP: Phrenic nerve pacing

DP: Intramuscular diaphragm pacing

SCS: Spinal cord stimulation

iSCS: Intercostal spinal cord stimulation

aSCS: Abdominal spinal cord stimulation

EMG: Electromyograph
SVM: Support vector machine
RBF: Radial basis function
IMU: Inertial measurement unit
SaPO₂: Oxygen saturation level
GUI: Graphical user interface
PCC: Pearson product-moment correlation coefficient
ANOVA: Analysis of variance
FFT: Fast fourier transform
MP: Motor point
RA: Rectus abdominis
EO: External oblique
CoR: Coefficient of repeatability
BoTN-A: Botulinum toxin A
EV: Exhaled volume
PF: Peak flow
RCT: Randomised control trial

Contributions

- In this thesis novel Abdominal Functional Electrical Stimulation (AFES) protocols and technologies are developed and implemented, and it is shown that they can help improve the respiratory function of the acute ventilator dependant and sub-acute tetraplegic population. Demonstration of the feasibility and effectiveness of these technologies and protocols is a necessary step towards the implementation of AFES as a clinical treatment modality. As such, a key contribution of this thesis is proof of feasibility.
- By using the respiratory data recorded from 10 able bodied participants a novel algorithm for non-intrusive real-time breathing pattern detection and classification has been designed and tested. The use of a non-intrusive sensor, coupled with an improved and less operator reliant classification algorithm, makes this method more suited to a clinical setting than previous work where the signal from an intrusive spirometer was used for breathing pattern classification.
- Neuromuscular electrical stimulation has been used for the first time to systematically detect the position of the motor points of the abdominal muscles. By applying single pulse electrical stimulation to the rectus abdominis and external oblique muscles, the position of the motor points of these muscles were successfully located in 10 able bodied and five tetraplegic participants. The position of the motor points of these muscles, along with the repeatability and uniformity of the position, is presented. The results of this study suggest that this method could be used to accurately detect the position of the abdominal muscle motor points to select the optimum electrode location for the application of AFES.
- In the main clinical study of this thesis the feasibility of using AFES to improve the respiratory function of acute ventilator dependant tetraplegics is shown. To use AFES with this patient group a number of adaptations to standard AFES protocols were required. Novel engineering solutions to allow AFES to be synchronised with mechanical ventilation, or with the user's own breathing, are presented. A novel training protocol, designed to improve respiratory function while allowing the effectiveness of AFES to be evaluated, was also developed. The gains in respiratory function achieved using these

novel technologies and protocols with 10 tetraplegic participants, who appeared to wean faster from mechanical ventilation than matched historic controls, suggest that acute ventilator dependent tetraplegic patients are a new treatment group who would benefit from the use of an AFES intervention during the early stage post-injury. The feasibility of using AFES to assist ventilator weaning for the chronic tetraplegic population who retain some diaphragm function is also demonstrated in a case study.

- Previous work has demonstrated that three weeks of AFES training with sub-acute and chronic tetraplegic participants did not appear to be sufficiently long to achieve the maximum benefit from an AFES training program. In this thesis the feasibility of using an eight week AFES training program to improve the respiratory function of people with sub-acute tetraplegia is demonstrated in a case series with three participants. The training effect shown in this study provides evidence for a potential future role of a prolonged AFES training program to improve the respiratory function of all tetraplegic participants.
- An engineering method to integrate AFES with mechanical insufflation-exsufflation, a clinical treatment modality commonly used to simulate cough and aid secretion clearance, is described and demonstrated in a case study with one sub-acute tetraplegic participant. These results indicate that, with a further refinement of the protocol and technology, the combination of these two treatment modalities could be used to help clear the airway of people with tetraplegia more effectively.

Publications

Journal Articles

1. E.J. McCaughey, A.J. McLachlan and H. Gollee, “Non-intrusive real-time breathing pattern detection and classification for automatic abdominal functional electrical stimulation,” *Med Eng Phys*, vol. 35, pp. 1057-1061, 2014.
2. E.J. McCaughey, A.N. McLean, D.B. Allan and H. Gollee, “Detection of the motor points of the abdominal muscles,” *Eur J Appl Physiol*, 10.1007/s00421-014-2966-y, 2014 .

In Preparation

1. E.J. McCaughey, A.N. McLean, D.B. Allan and H. Gollee “Abdominal Functional Electrical Stimulation to assist ventilator weaning in acute tetraplegia: A pilot study”
2. E.J. McCaughey, A.N. McLean, D.B. Allan and H. Gollee “Abdominal Functional Electrical Stimulation to enhance mechanical insufflation-exsufflation”

Conference Proceedings

1. E.J. McCaughey, H. Gollee, A.N. McLean, and D.B. Allan, “Detection of the motor points of the abdominal muscles,” *In Proceedings of UK BioEngineering 2013*, Glasgow, U.K., 2013.
2. E.J. McCaughey, H. Gollee, A.N. McLean, and D.B. Allan, “Abdominal functional electrical stimulation to assist ventilator weaning in tetraplegia,” *In Proceedings of 17th Annual International FES Society Conference*, Banff, Canada, 2012.
3. H. Gollee, A.J. McLachlan, E.J. McCaughey, A.N. McLean, M. Purcell, M. Fraser, and D.B. Allan, “Ventilator weaning supported by abdominal muscle stimulation in acute tetraplegia,” *In Proceedings of 51st Annual Scientific Meeting of the International Spinal Cord Society*, London, U.K., 2012.
4. E.J. McCaughey, A.J. McLachlan, and H. Gollee, “Breathing pattern detection and classification for automatic abdominal functional electrical stimulation,” *In Proceedings of 3rd Ann Conf of IFESS UKROI*, Birmingham, U.K., 2012.

5. E.J. McCaughey, A.J. McLachlan, and H. Gollee, “Breathing pattern detection for an abdominal functional electrical stimulation system for tetraplegics,” *In Proceedings of 6th IEEE EMBS UKROI Conf Bio Eng and Med Phys*, Glasgow, U.K., 2011.
6. E.J. McCaughey and H. Gollee, “A statistical classifier of breathing patterns for automatic abdominal muscle stimulation,” *In Proceedings of 2nd Ann Conf of IFESS UKROI*, Dublin, Ireland, 2011.
7. A.J. McLachlan, A.N. McLean, E.J. McCaughey, D.B. Allan, and H. Gollee, “Chest and abdomen motion during unassisted and FES assisted breathing in tetraplegia,” *In Proceedings of 2nd Ann Conf of IFESS UKROI*, Dublin, Ireland, 2011.
8. E.J. McCaughey and H. Gollee, “Development of a statistical classifier of breathing patterns for automatic abdominal muscle stimulation in tetraplegia,” *In Proceedings of IMechE 23rd Ann Med Eng Stud Proj Comp*, London, U.K., 2011.

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Chapter 1

Introduction

“If you can’t explain your physics to a barmaid it is probably not very good physics.”

Ernest Rutherford

1.1 Summary

Damage to the spinal cord, which results in a Spinal Cord Injury (SCI), is a life changing event that can have a profound effect on a person's quality of life. An injury to the cervical (neck) region of the spinal cord can cause paralysis or impaired function of all four limbs, a condition termed tetraplegia. In this chapter the prevalence of SCI is outlined, along with a description of the different classifications of SCI. How muscles work, along with the impact of tetraplegia on muscle function, particularly respiratory function, is described. Ways of measuring this respiratory function are also presented. The principles of Functional Electrical Stimulation (FES), with a focus on how it can be used to cause a contraction of paralysed muscles, are given. FES applied to the abdominal muscles, known as Abdominal Functional Electrical Stimulation (AFES), can be used to improve the respiratory function of people with tetraplegia and is described. This chapter concludes by outlining the aims of this thesis.

1.2 Spinal Cord Injury

The central nervous system is the part of the nervous system consisting of the brain and the spinal cord. An injury to the central nervous system can result in paralysis. A stroke, which is a loss of brain function due to a disturbance in blood supply to the brain, is the leading cause of paralysis in the United States of America (USA) [1]. Paralysis after stroke occurs due to the damaged brain no longer sending signals to muscles in the body. In the USA the second leading cause of paralysis, after stroke, is Spinal Cord Injury (SCI) [1]. Unlike a stroke, paralysis after SCI is caused by direct trauma to the spinal cord, resulting in a disruption in the pathway between a muscle and the brain. The effects of an SCI vary greatly. However, many people with SCI experience at least some loss of function (*i.e.* paralysis) and sensation. Advances in medical care over the last decades have resulted in increased survival rates and life expectancy for the spinal cord injured population [2]. This has led to an increase in the number of people living with an SCI, with the effective treatment of SCI, and its associated complications, becoming an increasingly important issue for society.

1.2.1 Prevalence

SCI most commonly affects young, active individuals, with the highest prevalence of new SCIs in people between 20 and 40 years of age [3]. The Spinal Injuries Association for the United Kingdom (UK) and Ireland estimates that there are over 40,000 people (0.06 percent of the UK population) living with an SCI in the UK¹. Of these 40,000, slightly over 3,000 reside in Scotland (0.06 percent of the Scottish population) [4]. In the year 2011-2012, there were 99 newly spinal cord injured patients admitted to the Queen Elizabeth National Spinal Injuries Unit (QENSIU) [4], the sole centre for treating SCIs in Scotland and one of 12 dedicated SCI centres in the UK. These 99 injuries represent an annual rate of 18 new SCIs

¹<http://www.spinal.co.uk/page/Some-basic-facts-about-SCI> (Accessed May 2014)

per million of population. In comparison, the National Spinal Cord Injury Statistical Center in the USA reported that in 2012, there were approximately 12,000 new cases of SCI in the USA², representing an annual rate of 37 new SCIs per million of population. Using the estimate developed by Lasfargues *et al.* [5], in 2013 there were approximately 270,000 people living with an SCI in the USA. This represents approximately 0.08 percent of the American population, correlating with the data from the UK.

The etiology of an SCI can be classed as either traumatic or non traumatic. The most common causes of non traumatic SCI are spinal multiple sclerosis, cervical spondylosis (spinal stenosis) and amyotrophic lateral sclerosis (motor neuron disease), with tumour compression, infectious abscesses and vascular malformations less common causes [6, 7]. Traumatic SCIs result from trauma to the spinal cord. In the UK falls are the leading cause of traumatic SCI, followed by Road Traffic Accidents (RTAs) and sporting injuries [4]³. In contrast, RTAs are the primary cause of traumatic SCI in the USA, followed by falls and violence [8]. The etiology of traumatic SCIs in Scotland, the UK and the USA is shown in Table 1.1.

Table 1.1: Number of traumatic spinal cord injuries in Scotland, the United Kingdom (UK) and United States of America (USA) caused by falls, Road Traffic Accidents (RTAs), sports and other etiologies in 2012. Results are expressed as a percentage of all reported traumatic spinal cord injuries.

Region	Year	Causes			
		Falls	RTA	Sports	Others
Scotland	2012	55%	21%	8%	16%
UK (inc. Scotland)	2012	46%	39%	10%	5%
USA	2012	21%	44%	10%	25%

Traumatic SCIs have a greater prevalence in males than females, with multi center studies showing a male to female ratio of approximately four to one [9, 10]. Compared to traumatic SCIs, non traumatic SCIs are associated with an older age at injury [11] and have an almost equal prevalence amongst males and females [12]. Of the 99 patients admitted to the QENSIU in 2011-2012 with an SCI, 35 percent ($n = 35$) had an SCI of a non traumatic nature [4]. This agrees with the findings of other incidence studies [11, 13], where approximately one third of SCIs were found to have a non traumatic etiology.

1.2.2 Anatomy of the Spinal Cord

Humans are born with 33 vertebrae in the spinal column, consisting of seven cervical vertebrae, 12 thoracic vertebrae, five lumbar vertebrae, five sacral vertebrae and four coccygeal vertebrae. The cervical, thoracic and lumbar vertebrae are separated by intervertebral discs, which are not present between the sacral or coccygeal vertebrae. This leads to both the sacral and coccygeal vertebrae fusing in adult life to form two bones, known

²<https://www.nscisc.uab.edu/> (Accessed May 2014)

³<http://www.spinal.co.uk/page/Some-basic-facts-about-SCI> (Accessed May 2014)

as the sacrum and coccyx (or tailbone). In adult humans the cervical vertebrae are located in the neck, the thoracic vertebrae are located between the shoulders and middle back and the lumbar vertebrae are situated in the lower back, above the sacrum and the coccyx. These vertebrae are shown in Figure 1.1.

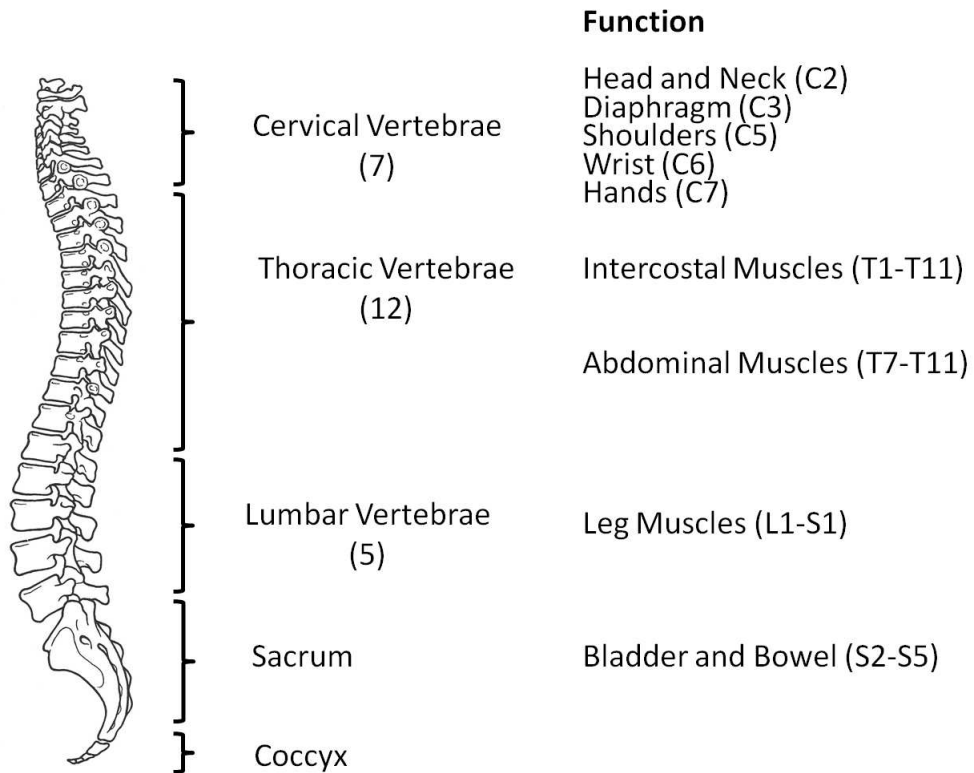


Figure 1.1: Vertebrae of the adult spinal cord, highlighting the cervical, thoracic and lumbar vertebrae, along with the sacrum and the coccyx. Also shown is the level of the spinal cord from which the nerves emanate that control various muscles and functions of the body.

Humans have 31 left-right pairs of spinal nerves, which carry motor, sensory and autonomic signals between the spinal cord and the body. These consist of eight cervical nerve pairs (C1-8), 12 thoracic pairs (T1-12), five lumbar pairs (L1-5), five sacral pairs (S1-5) and one coccygeal pair. These spinal nerves exit the spinal cord between adjacent vertebrae, except for the first cervical nerve, referred to as C1, which exits above the first cervical vertebrae. Therefore, the cervical nerves are all numbered according to the vertebrae below the nerve, except for C8 which exists between C7 and T1, while the thoracic, lumbar and sacral nerves are all numbered according to the vertebrae above.

1.2.3 Paralysis

There are two main factors that determine the severity of an SCI, namely the injury level and completeness of injury.

1.2.3.1 Injury Level

The neurological level of injury is defined in the International Standards for Neurological Classification of Spinal Cord Injury as ‘the most caudal segment of the spinal cord with normal sensory and antigravity motor function on both sides of the body’ [14]. Neurological level is often further defined by both sensory and motor levels. The International Standards describe the sensory level as ‘the most caudal, normally innervated dermatome for both pin prick and light touch sensation’ and the motor level as ‘the lowest key muscle function that has a grade of at least three’ (see Table 1.2 in Section 1.2.3.2 for more information on muscle scoring). The sensory and motor level of an SCI can differ, as can the sensory or motor level on either side of the body. When the scores differ on either side of the body, the different levels are reported individually. An injury level reported as C5/6 would imply an injury level of C5 on one side of the body and C6 on the other. The level at which skeletal damage to the vertebrae occurs, termed skeletal level, may differ from the neurological level of injury.

Different muscles are innervated from descending levels of the spinal cord, as shown in Figure 1.1. The more cranial the level of injury the more severe the impairment after SCI, as a larger number of muscles will no longer be capable of being innervated from the spinal cord.

1.2.3.2 Completeness of Injury

The severity of an SCI is commonly described using the five level American Spinal Injuries Association (ASIA) Impairment Scale (AIS), based on the degree of sensory and motor sparing. According to the AIS, an injury is sensory and motor complete, classed as AIS A, if there is no function or sensation in muscles controlled by the nerves emanating from the spinal cord at S4-S5. As these are the most caudal nerves emanating from the spinal cord that are responsible for movement (the coccygeal nerve is only responsible for sensation), any function or sensation in the muscles controlled by these nerves indicates that the pathway between the brain and the most caudal portion of the spinal cord is still intact and that the injury is incomplete. If sensation, but not function, is preserved below the injury, the injury is classified as sensory incomplete, and classed as AIS B. If function and sensation is preserved below the level of injury, the injury is defined as motor and sensory incomplete and classed from AIS C to AIS E based on the level of muscle function. To determine this level of muscle function a range of movement tests are performed, either against gravity or with caregiver support depending on the level of impairment. Muscles are scored and classed using the six point scale described in Table 1.2. The chart used to record AIS is shown in Figure 1.2.

Traditionally it was believed that a complete SCI severed the connection between the brain and the spinal cord, preventing any signals from the brain reaching their destination. An incomplete SCI was believed to disrupt the path from the brain to the spinal cord, with some signals still able to reach their destination. It is now emerging that even in complete SCI some signals may travel through the damaged site in the spinal cord [15]. Although these signals do

Table 1.2: Explanation of ASIA Impairment Scale (AIS) muscle function scoring scale [14]. If more than 50% of the key muscle groups below the neurological level of injury have a score of less than 3, the injury is classed as AIS C. If more than 50% of the key muscle groups have a score ≥ 3 , the injury is classed as AIS D. If function and sensation are normal this is classed as AIS E

Muscle score	Definition	AIS Level
0	Total paralysis.	C
1	Palpable or visible contraction.	
2	Active movement, full range of motion (ROM) with gravity eliminated.	
3	Active movement, full ROM against gravity.	D
4	Active movement, full ROM against gravity and moderate resistance in a muscle specific position.	
5	(Normal) active movement, full ROM against gravity and full resistance in a muscle specific position expected from an otherwise unimpaired person.	E

Patient Name _____
 Examiner Name _____ Date/Time of Exam _____

ASIA INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY **ISCOS**

MOTOR
 KEY MUSCLES (scoring on reverse side)

	R	L
C5		
C6		
C7		
C8		
T1		

UPPER LIMB TOTAL (MAXIMUM) (25) (25) (50)

Comments:

KEY MUSCLES
 Elbow flexors
 Wrist extensors
 Elbow extensors
 Finger flexors (distal phalanx of middle finger)
 Finger abductors (ring finger)

SENSORY
 KEY SENSORY POINTS

0 = absent
 1 = altered
 2 = normal
 NT = not testable

NEUROLOGICAL LEVEL
 The most caudal segment with normal function

SINGLE NEUROLOGICAL LEVEL

COMPLETE OR INCOMPLETE?
 Incomplete = Any sensory or motor function in S4-S5

ASIA IMPAIRMENT SCALE (AIS)

ZONE OF PARTIAL PRESERVATION
 Most caudal level with any innervation

Key Sensory Points

• Key Sensory Points

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Figure 1.2: ASIA Impairment Scale scoring chart (taken from <http://asia-spinalinjury.org/> in May 2014).

not result in movement, believed to be because their amplitude is below the threshold required to generate an action potential (see Section 1.3), they do reach their destination. As there is no movement, or function, these injuries can be described as functionally complete. It appears that almost no SCI is neurologically complete, whereby there is no connection between the

brain and a muscle. Approximately 50 percent of SCIs are classed as complete [16]. Whether an SCI is complete or incomplete can have a large effect on a patient's rehabilitation and their neurological, functional and social outcomes [17].

Patients with an SCI can also be grouped according to the time after injury. Acute SCI generally refers to the immediate post-injury period when there is continuing tissue damage and the patient is in spinal shock. Spinal shock causes an immediate loss of reflexes and resulting flaccid paralysis in the muscles below the level of injury that return over time [18]. The acute phase of injury generally lasts for up to four weeks [19]. During the phase where the spinal cord undergoes a reparative process and there is continuing neurological recovery an SCI can be classified as sub-acute. The sub-acute phase typically begins around four weeks after injury and continues for three to six months. When inflammation has stabilised and neurological recovery has reached a plateau an SCI can be classified as chronic, which typically does not occur until three to six months after injury [20]. While there is debate as to the exact time frame for these classifications [21], within this thesis acute SCI will be defined as any SCI up to four weeks post injury, sub-acute SCI will be defined as any SCI between four weeks and three months post injury and chronic SCI will be defined as any SCI greater than three months post injury.

1.2.4 Tetraplegia

An injury to the spinal cord in the cervical (C1 to C7) region can cause tetraplegia⁴. Tetraplegia is defined as 'impairment or loss of motor and/or sensory function in the cervical segments of the spinal cord' [14], and results in paralysis or impairment of all four limbs. An injury to the spinal cord in the thoracic or lumbar region can cause paraplegia. Paraplegia is defined as 'impairment or loss of motor and/or sensory function in the thoracic, lumbar or sacral (but not cervical) segments of the spinal cord' [14], and results in paralysis or impairment of the legs. Due to the paralysis affecting all four limbs, tetraplegia is a more serious injury than paraplegia, with the extent of remaining upper limb function depending on the neurological level of injury. Approximately half of all SCIs result in tetraplegia, although the exact figure has been increasing in recent years with one study finding that 56.6 percent of SCIs resulted in tetraplegia between 2000 and 2003 compared to 53.5 percent between 1973 and 1979 [22]. This rise can be attributed to improved medical care, which has led to increased survival rates at the scene and in hospital, for people with tetraplegia.

Tetraplegia is associated with a significantly higher health care cost than paraplegia [22]. A primary reason for this is that tetraplegia leaves patients particularly susceptible to secondary complications of SCI, such as chronic pain, bladder and bowel dysfunction, pressure ulcers, autonomic dysreflexia and respiratory complications [23, 24]. These secondary complications place a large financial burden on the local health care provider [25] and are attributed to approximately 30 physician visits per year [26]. As well as these high costs, secondary

⁴Tetraplegia is commonly referred to as quadriplegia in the USA

complications can also leave the patient with a perceived reduction in their quality of life [27]. Of these secondary complications, respiratory complications are a leading cause of morbidity and mortality for the tetraplegic population [2, 28, 29, 30]. Therefore, a reduction in the rates of respiratory complications will improve the patient's quality of life and reduce the financial burden on the local health care provider.

For people with tetraplegia, secondary complications have a different prevalence depending on whether the etiology of the injury is traumatic or non traumatic [31]. However, the prevalence of respiratory complication observed in the acute care and rehabilitation setting are similar for both cases [13]. Therefore, this thesis, which will seek methods to reduce the prevalence of respiratory complications and improve respiratory function in the tetraplegic population in the acute care setting, will make no distinction between traumatic and non traumatic SCIs.

1.3 Muscle Anatomy

The human body contains three types of muscle; skeletal, cardiac and smooth. Of these three muscle types, skeletal muscle is the only one that is under voluntary control and as such will be the only muscle type discussed in this thesis.

Each muscle of the body is supplied by a nerve that contains motor, sensory and sympathetic nerve cells, used to supply movement, sensation and control the autonomic nervous system, respectively. The nerve cells that control movement are called motor neurons and can be split into Upper Motor Neurons (UMNs) and Lower Motor Neurons (LMNs). UMNs carry motor information from the brain to the spinal cord, while LMNs branch out from the spinal cord to carry motor information to different muscles as shown in Figure 1.3.

A lesion that affects either the UMNs or LMNs will result in a decrease or loss of voluntary control of the muscles that they supply. Due to a lack of inhibition of the reflex pathways, normally provided by the UMNs, an UMN lesion causes hyperactive or abnormal reflexes. This results in spastic paralysis, which increases muscle tone. An UMN lesion occurs in approximately 50 percent of SCIs [16], causing a motor complete SCI where paralysis affects all the muscles innervated below this lesion.

Due to damage of the reflex pathways an LMN lesion causes absent or decreased reflexes. This results in flaccid paralysis, which decreases muscle tone. In SCI an LMN lesion is observed either i) at the point where the LMNs exit the spinal cord or ii) to the nerves away from the spinal cord. LMN lesions at the spinal cord are usually caused by fractured vertebrae damaging the nerve, with SCIs in the upper cervical area (C5 and above) particularly prone to an LMN lesion caused by this method. An LMN lesion to the nerves away from the spinal cord is especially common for the nerves that exit through the vertebrae of the lower lumbar spine (L3 and below), where the LMNs are again damaged due to severe fractures of

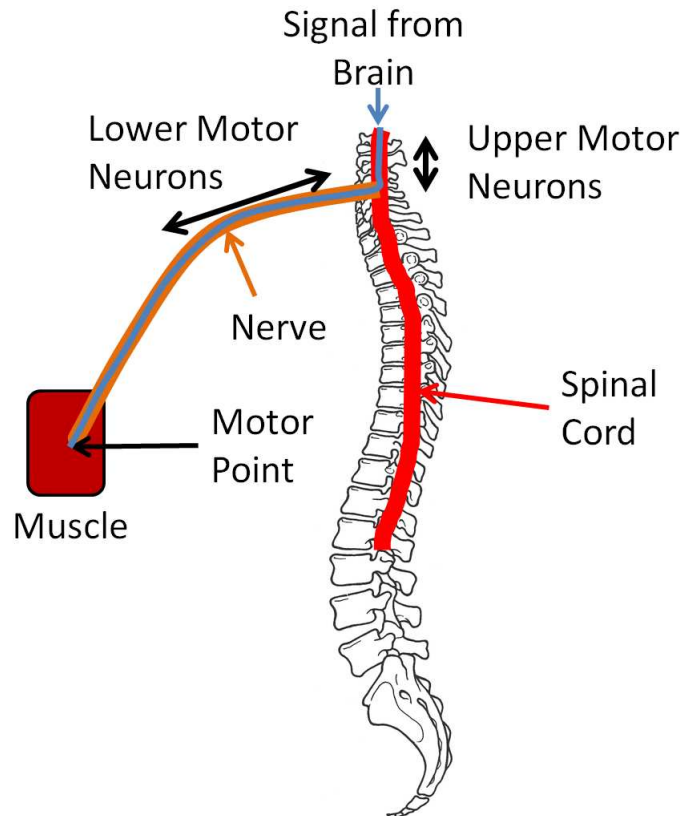


Figure 1.3: Diagram of the route of a motor signal (light blue) from the brain to a muscle. The signal passes from the brain down the spinal cord (red) via Upper Motor Neurons. It then travels down a nerve (orange) via Lower Motor Neurons, before entering a muscle. The point at which a nerve enters a muscle is called the motor point.

these vertebrae. An LMN lesion usually presents as localised weakness of muscles innervated by nerves affected by the lesion. Importantly, as the use of electrical stimulation to cause a muscle contraction requires an intact pathway between the stimulated nerve and its associated muscle, electrical stimulation cannot be used to cause a muscle contraction in the presence of LMN damage. Therefore, electrical stimulation will only be used with patients who have not suffered LMN damage within this thesis.

The neuromuscular junction, or motor point, is the location where a nerve enters a muscle as shown in Figure 1.3. A muscle is made up of contractile cells, often called fibres as they are so long, which are joined by connective tissue. Skeletal muscle fibres can be divided into two categories, Type I (slow twitch) and Type II (fast twitch). Type I fibres contain large amounts of myoglobin, a protein found in muscles that carries oxygen. Therefore, Type I fibres have a large supply of oxygen. Type II fibres contain only small amounts of myoglobin and hence oxygen. Type I fibres are smaller than Type II fibres and are largely fatigue resistant due to their large supply of oxygen, while the decreased oxygen supply to a Type II fibre results in rapid fatigue. Type I fibres are designed for endurance, while Type II fibres are designed for power and speed. The percentage of each type of muscle fibre within the

body varies from person to person. Typically sprint athletes will have more Type II fibres, while endurance athletes will have more Type I fibres. The combination of an LMN with all of its corresponding muscle fibres is called a motor unit. Motor units can vary in size from small units, with small diameter axons, to large units, with larger diameter axons. Small motor units, which contain only a few fibres, are used to achieve precise movements. The activation of additional larger motor units results in a larger muscle contraction, allowing more powerful tasks to be executed. All motor units contain only one type of muscle fibre. Small motor units tend to be made up of Type I muscle fibres, with larger motor units more likely to be made up of Type II muscle fibres. Henneman's size principle states that the natural recruitment order of motor units is from smallest to largest (fewest fibres to most fibres) [32].

In the able bodied population a muscle contraction is activated by an electrical signal sent from the brain, via the spinal cord, to the nerve controlling the muscle as shown in Figure 1.3. This electrical signal creates an action potential, a short lasting increase in electrical potential of a cell, which starts a chain of electrochemical events that cause a muscle contraction. A muscle can be made to contract in two ways. When a single stimulus of adequate strength is applied to a muscle this generates a twitch contraction. If stimulation pulses are delivered at a frequency of greater than 12.5 Hz this generates a constant tetanic contraction because the muscle does not have time to relax between individual twitches.

1.4 Respiratory Function

Respiration, or breathing, provides oxygen to the body and removes carbon dioxide. As air naturally resides in the area of lowest pressure, the respiratory muscles are used to increase or decrease the pressure around the lungs, called the intrathoracic pressure. The decrease of intrathoracic pressure to a pressure lower than that outside the body causes air to flow into the lungs, a process called inhalation. An increase in the intrathoracic pressure to a pressure greater than that outside the body causes air to flow out of the lungs, a process called exhalation.

The two most common types of breathing are quiet breathing and coughing. A cough is used to clear the airway, while a quiet breath is taken during normal relaxed breathing. To generate the power required to clear the airways, a cough has a greater peak expiratory air flow rate than a quiet breath, with this peak flow rate reached earlier in the exhalation. The exhalation length of a cough is often shorter than the exhalation length of a quiet breath. The difference between these two breath types is shown in Figure 1.4.

1.4.1 Respiratory Muscles

The main muscles used for respiration are the diaphragm and the intercostal and abdominal muscles, with the location of each of these muscles shown in Figure 1.5.

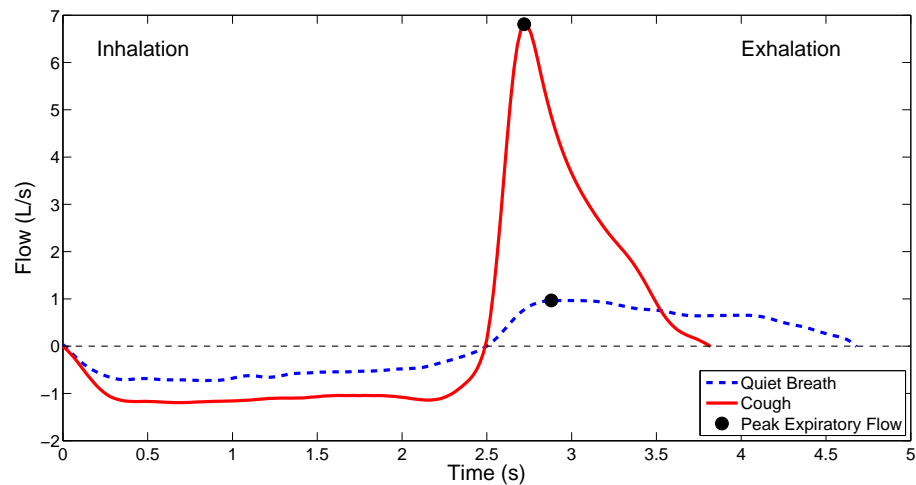


Figure 1.4: A measurement of respiratory flow, recorded using a spirometer, highlighting the difference in peak expiratory flow rate, and the time point where this peak expiratory flow rate occurs, during quiet breathing (blue) and coughing (red).

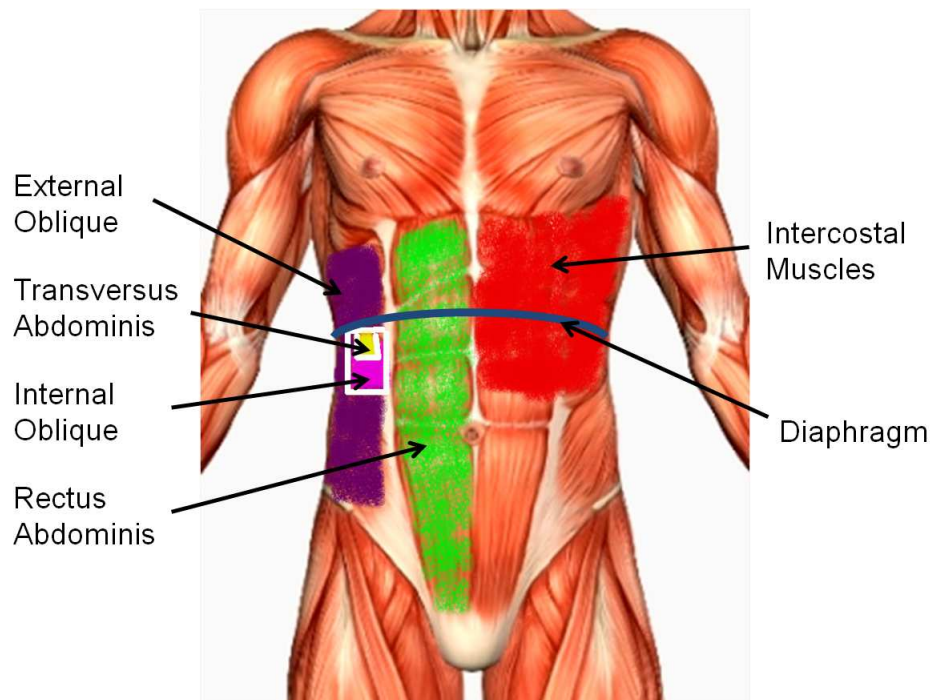


Figure 1.5: Respiratory muscle anatomy. Highlighted are the rectus abdominis muscles (green), the external oblique muscles (purple), the internal oblique muscles (pink), which are situated under the external oblique muscles, and the transversus abdominis muscles (yellow), which are situated under the internal oblique muscles. These muscles are situated in the same location on both sides of the body and make up the abdominal muscles. The intercostal muscles (red), which are interwoven around the ribs on both sides of the body, and the diaphragm (blue) are also shown.

The diaphragm is situated across the bottom of the rib cage, separating the thoracic and abdominal cavity, and takes the form of a dome shaped thin layer of muscle. The diaphragm aids inspiration by contracting to increase the volume of the thoracic cavity, reducing the intrathoracic pressure and causing an inhalation. The diaphragm is responsible for approximately 65 percent of a persons vital capacity (see Section 1.4.2) [33].

During quiet breathing, exhalation is passive. The return of the diaphragm to its original position, coupled with the elastic recoil of the lungs, acts to increase intrathoracic pressure and cause exhalation. A forced exhalation, such as that observed during exercise or coughing, is an active process. During a forced exhalation, a contraction of the intercostal and abdominal muscles, coupled with the return of the diaphragm to its original position and the elastic recoil of the lungs, increases the intrathoracic pressure, causing exhalation.

The intercostal muscles are a network of interwoven muscles, located between the ribs. They are composed of the external, internal and innermost intercostal muscles, and are innervated by 24 separate nerves. Each nerve innervates muscles that have both an inspiratory and expiratory function. The external intercostal muscles aid inhalation by pulling the ribcage upwards and outwards, increasing the diameter of the chest and decreasing intrathoracic pressure. The internal and innermost intercostal muscles aid forced exhalation by pulling the ribcage downwards and inward, increasing intrathoracic pressure. The intercostal muscles are responsible for approximately 35 percent of a persons vital capacity [34].

The abdominal muscle group consists of four muscles situated within the abdomen, namely the transversus abdominis, the rectus abdominis and the internal and external oblique muscles. The location of these muscles within the abdominal cavity is shown in Figure 1.5. The abdominal muscles support forced exhalation by drawing the abdominal contents inward, increasing intrathoracic pressure and pushing the diaphragm upwards.

The diaphragm is innervated by the phrenic nerve, originating from the spinal cord at C3 to C5. The intercostal muscles are innervated by the intercostal nerves, originating from the spinal cord at T1 to T11, and the abdominal muscles are innervated by the thoracoabdominal nerves, originating from the spinal cord at T7 to T11. People with motor complete tetraplegia will have paralysed intercostal and abdominal muscles. If the neurological level of injury is C3, C4 or C5 they will have impaired diaphragm function. If the neurological level of injury is C1 or C2 they will have no diaphragm function and will be unable to breathe independently. Damage to the LMNs within the phrenic, intercostal or thoracoabdominal nerves would result in an inability to activate the diaphragm, intercostal or abdominal muscles respectively.

1.4.2 Measures of Respiratory Function

A number of measures can be used to evaluate the status of a persons respiratory function, with these measures varying between people depending on sex, age, height and weight [35].

A summary of these respiratory measurements is presented in Table 1.3, with each of these respiratory measurements explained in further detail in this section.

Table 1.3: Summary of different measurements of respiratory function. The acronym used for each measure throughout this thesis, what the tests measure and whether this measure relates to the strength of the inspiratory or expiratory muscles is given.

Measurement	Acronym	Measurement of	Muscles
Peak Expiratory Flow	PEF	Maximum Expiratory Flow Rate During Normal Breath	Expiratory
Cough Peak Flow	CPF	Maximum Expiratory Flow Rate During Cough	Expiratory
Maximum Expiratory Pressure	MEP	Maximum Pressure During Exhalation	Expiratory
Maximum Inspiratory Pressure	MIP	Maximum Pressure During Inhalation	Inspiratory
Forced Vital Capacity	FVC	Actively Exhaled Volume	Inspiratory
Vital Capacity	V_C	Passively Exhaled Volume	Inspiratory
Forced Exhaled Volume in 1 Second	FEV ₁	Actively Exhaled Volume in First Second	Expiratory
Tidal Volume	V_T	Exhaled Volume of Normal Breath	Inspiratory

The volume of air exhaled in each normal breath is called Tidal Volume (V_T), and is measured in litres (L). A healthy adult has an V_T of approximately 0.5 L [36, 37]. To normalise respiratory function across a group weight corrected tidal volume (V_T/kg), which is a persons V_T divided by their body weight, is often reported [38, 39] and will be used for all group comparisons in this thesis.

Respiratory failure leads to some patients with tetraplegia requiring mechanical ventilation, a method to assist or replace spontaneous breathing (see Section 2.3.1 for more information). V_T plays an important role during mechanical ventilation, with a V_T/kg of approximately 8 to 15 ml/kg applied to ensure adequate ventilation [38]. During mechanical ventilation, an V_T/kg of greater than 15 ml/kg has been linked to complications such as barotrauma (alveolar rupture due to high pressure) and pulmonary edema (fluid accumulation in the lungs). However, some research suggests that a high V_T/kg may be useful in treating atelectasis (collapse of part of the lung), a common complication after SCI [39].

Cough Peak Flow (CPF) is the maximum rate at which a person can exhale air from their lungs during a cough, while Peak Expiratory Flow (PEF) is the maximum rate at which a person can exhale air from their lungs when exhaling as forcefully and as quickly as possible. As both CPF and PEF are measures of the rate at which air leaves the lungs, both can be used to detect obstruction of the airways. As both are taken during an active exhalation,

whereby the participant actively exhales, they also give an indication of the strength of the expiratory muscles. Both CPF and PEF are measured in litres per second (L/s), although litres per minute (L/min) may sometimes be reported. An example of a typical PEF trace recorded from a healthy adult male and female is shown in Figure 1.6.

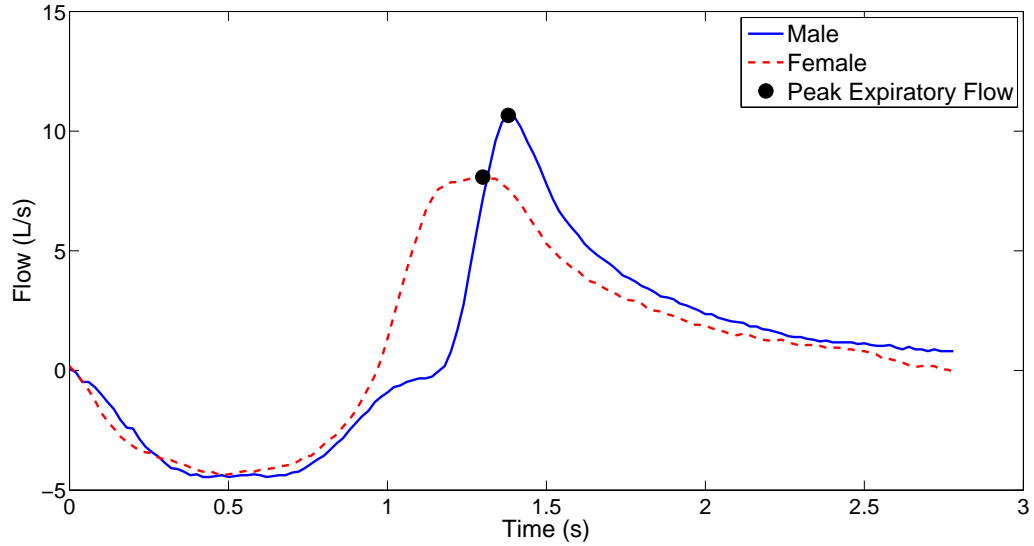


Figure 1.6: Peak Expiratory Flow (marked with black circle) recorded from a healthy, 183 cm tall, 26 year old male (blue) and a healthy, 170 cm tall, 26 year old female (red).

Maximum Expiratory Pressure (MEP), the maximum pressure generated against resistance during an exhalation, can be used to measure the strength of the expiratory muscles, while Maximum Inspiratory Pressure (MIP), the maximum pressure generated against resistance during an inhalation, can be used to measure the strength of the inspiratory muscles. Both MEP and MIP are recorded using a pressure meter and are measured in centimeters of water (cmH₂O). For males MEP and MIP vary depending on age, while for females MEP and MIP vary depending on height [40].

As well as the aforementioned flow and pressure measurements, respiratory function can also be evaluated using a number of volumetric measurements, with some of these measurements shown in Figure 1.7.

Vital Capacity (V_C), the total volume of air exhaled after inhaling to total lung capacity and exhaling passively, and Forced Vital Capacity (FVC), the total volume of air exhaled after inhaling to maximum lung capacity and exhaling as forcefully as possible, can be used to evaluate the strength of the inspiratory muscles [41]. For people with tetraplegia, severe impairment or paralysis of the respiratory muscle prevents them from inhaling to total lung capacity. This results in people with tetraplegia only being able to inhale to a percentage of their lung capacity, denoted here as their functional lung capacity. V_C and FVC can be used to assess the degree of respiratory muscle impairment after SCI. In this thesis, tetraplegic patients will be asked to inhale as fully as possible, to what will be their functional lung

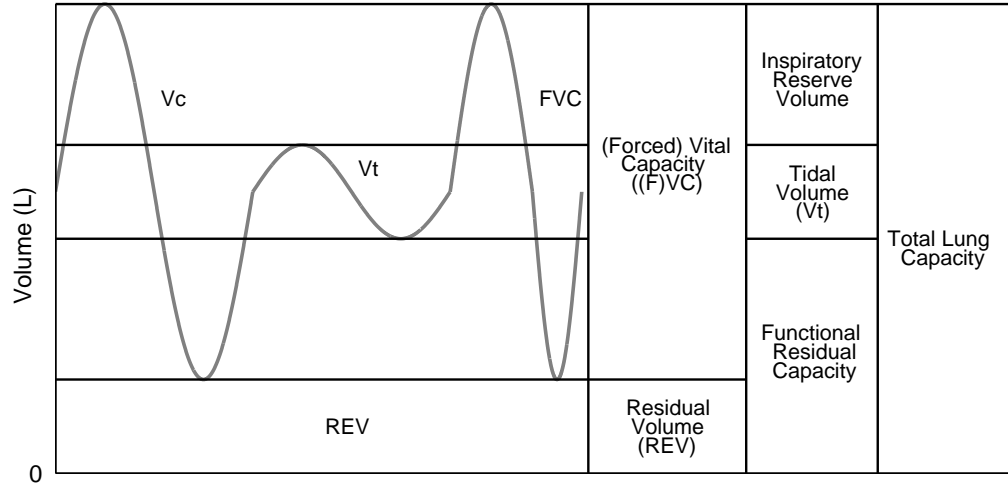


Figure 1.7: Example respiratory measurements highlighting: Forced Vital Capacity (FVC), Vital Capacity (V_C), Tidal Volume (V_T), Residual Volume (REV) (the volume of air which permanently resides in the lungs), total lung capacity (the maximum volume of the lungs), inspiratory reserve volume (the additional volume of air that can be inhaled at the end of a normal inhalation) and functional residual capacity (the volume of air which remains in the lungs after a normal exhalation).

capacity, and then exhale fully to establish V_C and FVC. As FVC is recorded during an active exhalation, the exhalation length during an FVC manoeuvre is normally shorter than when measuring V_C , as shown in Figure 1.7. Both FVC and V_C are measured in L, with only a small difference in the values recorded from both tests. As with V_T , to allow a comparison between different people weight corrected forced vital capacity (FVC/kg) and weight corrected vital capacity (V_C/kg) are often reported [42], and will be used for all group comparisons in this thesis.

From an FVC manoeuvre, the Forced Exhaled Volume in one second (FEV_1) can also be measured. FEV_1 , which is the volume of air which can be exhaled from the lungs in the first second of a forced exhalation, provides an indication of the strength of the expiratory muscles. FEV_1 is measured in L/s, and is approximately 80 percent of a persons FVC [43]. An example of an FVC and FEV_1 recording is shown in Figure 1.8.

All of the aforementioned measures of respiratory function, except for MIP and MEP which require a pressure meter, can be recorded using a spirometer, which is a device use to measure the volume, or flow, of air inhaled and exhaled by the lungs. PEF is also often measured using a peak flow meter. Miller *et al.* [44] have shown that peak flow meters can have a large inter device variability, hence the use of a spirometer is now becoming the ‘gold standard’ for PEF measurement. The predicted values of respiratory function for a healthy 30 year old male and female are shown in Table 1.4.

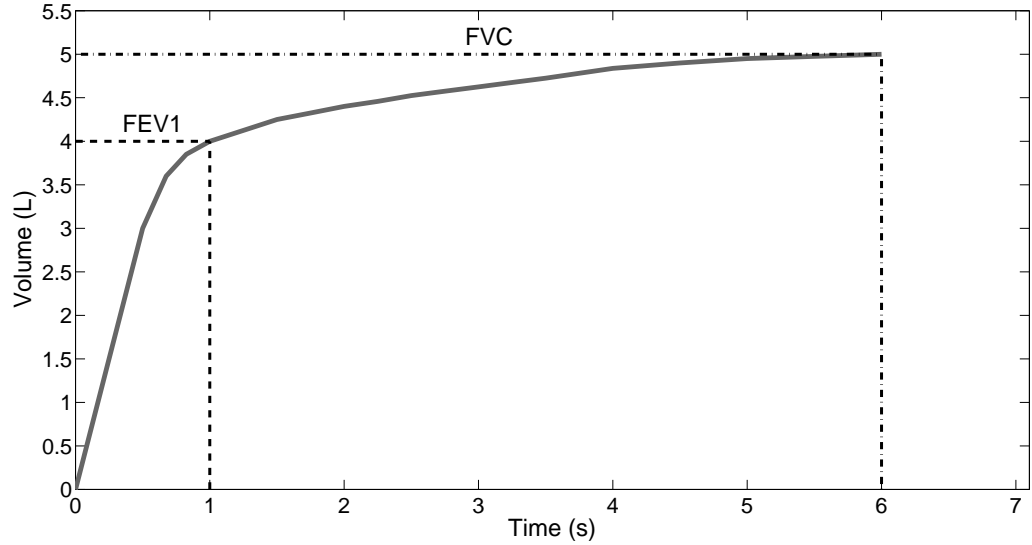


Figure 1.8: Example of Forced Exhaled Volume in one second (FEV_1) recorded during a Forced Vital Capacity (FVC) manoeuvre recorded from a 170 cm tall, 30 year old male.

Table 1.4: Predicted values of Peak Expiratory Flow (PEF), Maximum Expiratory Pressure (MEP), Maximum Inspiratory Pressure (MIP), Forced Vital Capacity (FVC), Forced Exhaled Volume in one second (FEV_1) and Tidal Volume V_T for a healthy, 180 cm tall, 30 year old male and a healthy, 160 cm tall, 30 year old female [35, 37, 40, 43].

Respiratory Measure	Male	Female
PEF	10.5 L/s	6.8 L/s
MEP	153 cmH ₂ O	91 cmH ₂ O
MIP	111 cmH ₂ O	71 cmH ₂ O
FVC	5.6 L	3.7 L
FEV_1	4.6 L/s	3.1 L/s
V_T	0.5 L	0.4 L

1.4.3 Respiratory Function in Tetraplegia

Paralysis, or severe impairment, of the main respiratory muscles leaves many people with tetraplegia with reduced respiratory function. A person with tetraplegia is likely to have an FVC of less than 50 percent of the predicted value for a healthy adult, and a reduced V_T [30]. This reduced respiratory function leaves many people with tetraplegia unable to effectively clear their airways through cough, leading to a build up of secretions in the lungs and airways and making people with tetraplegia prone to respiratory infections. These respiratory infections often lead to the development of respiratory complications such as pneumonia (inflammation of the alveoli often caused by respiratory infection) and atelectasis (collapse or closure of the lung resulting in poor gas exchange often caused by a mucus plug in the lungs). Dryden *et al.* found that in a six year follow up study, 33.8 percent of people with an SCI developed at least one case of pneumonia [45]. This increased susceptibility to

respiratory complications makes them a leading cause of morbidity and mortality for people with tetraplegia [28], while placing a cost burden on the local health care provider [25].

Mechanical ventilation reduces a patient's quality of life, delays rehabilitation and places a large financial burden on the local health care provider [27]. Dasta *et al.* estimate that mechanical ventilation costs the health care provider an additional \$1500 per day based on the USA hospital system [46]. People with tetraplegia who have a very high level complete injury (C2 and above) will have no diaphragm function (see Section 1.4.1). For these patients chronic use of mechanical ventilation is necessary to support respiratory function. For many other tetraplegic patients who retain some diaphragm function (injury C3 and below) mechanical ventilation is required to assist respiration in the acute stage of injury due to respiratory failure [47]. Most of these patients require only short periods of mechanical ventilation and will wean from ventilation within a number of weeks. For some, particularly those with a greater reduction in diaphragm function, the weaning process can take longer and sometimes requires the chronic use of mechanical ventilation. As these patients retain some level of diaphragm function, and hence have the ability to breathe independently, with assistance they should eventually wean from ventilation.

It is clear that an improvement in the respiratory function of people with tetraplegia would not only improve the patient's quality of life, but would also result in a significant cost saving for the local health care provider.

“Improvements in respiration and the elimination of ventilator-dependence are extremely important to the quality of life, and this topic should be at the forefront of research.”

Kim Anderson [48]

Therefore, the poor respiratory function of the spinal cord injured population requires to be addressed.

This is currently achieved clinically using a number of methods. For those who lack the ability to breathe independently due to severely impaired diaphragm function mechanical ventilation is the clinically accepted method to assist respiration. This can be applied either invasively, by attaching the ventilator to a endotracheal or tracheostomy tube, or non-invasively, using an orofacial mask. For those who retain the ability to breathe spontaneously but have reduced respiratory function resulting in an ineffective cough manually assisted coughing, mechanical insufflation-exsufflation or tracheal suctioning are all used to simulate a cough and clear secretions from the airways. For these patients, respiratory muscle training, which typically uses restrictive air flow devices to train the muscles used for inspiration and expiration, is also used clinically to try and improve respiratory function. As discussed in Chapter 2, none of these methods are a panacea, with a non-invasive, reliable alternative still to be introduced clinically.

1.5 Functional Electrical Stimulation

Neuromuscular Electrical Stimulation (NMES) is the application of a train of electrical pulses to a motor nerve, causing contraction of the associated muscle. NMES can be used in health care for one of three purposes: to aid diagnosis, as a therapeutic tool, and/or to restore lost or damaged function [49]. The concept of Functional Electrical Stimulation (FES) was first proposed by Liberson *et al.* [50] to describe the use of NMES to activate muscles in a precise sequence to achieve a functional task, in this case for the correction of foot drop, alluding to the third of these health care uses. Transcutaneous Electrical Nerve Stimulation (TENS) also comes under the canopy of NMES. Unlike FES, TENS is used as a therapeutic treatment without a functional outcome, primarily being used for pain relief.

1.5.1 Principles of FES

For people who have paralysis that does not result in LMN damage, the pathways from the spinal cord to the nerves remain intact below the level of injury (*i.e.* below the neurological level of injury in SCI and below the level of the brain in stroke). This means that although a muscle may be paralysed and no longer under voluntary control, it still retains the ability to contract. FES can be used to provide an electrical signal to a nerve, which generates an action potential and causes these paralysed muscles to contract. Note, electrical stimulation is applied to the nerve rather than the muscle itself as the stimulation threshold required to generate a nerve fibre action potential is significantly lower than that required to generate a muscle fibre action potential. FES may also be used to initiate a reflex, rather than muscle, response, such as when stimulating the peroneal nerve to initiate the nociceptive withdrawal reflex and correct foot drop.

When using FES to achieve a muscle contraction, the optimum muscle contraction is usually observed when stimulation is applied close to the motor point of the muscle (see Section 1.3) [51]. Studies have shown that placing the stimulating electrodes at the motor point maximises force output and minimises discomfort [52, 53]. In implanted systems stimulation may be applied to the nerve directly, away from the motor point, to achieve a similar effect. The effect that FES has on the way muscles are recruited is less clear. It is believed that the use of FES leads to a ‘reverse recruitment order’, where larger diameter, Type II (see Section 1.3), motor units are recruited preferentially to smaller diameter, Type I, motor units [51, 54]. According to Bickel *et al.* [55], the theory of ‘reverse recruitment order’ is based on the finding that FES appears to lead to faster muscle fatigue than normal muscle recruitment. This appears to indicate that large motor units, which are more easily depolarised (depolarisation is the process required to generate an action potential) [55] and are more prone to fatigue than smaller motor units, are being recruited preferentially. Bickel *et al.* argue that motor unit recruitment with FES is actually random, with motor units being recruited in a non selective way. They state that increased levels of muscle fatigue observed during FES is caused by the repeated application of the same stimulation parameters

continuing to recruit the same motor units. Whether FES does follow the reverse recruitment order or activates motor units at random, it is working differently to the body's natural recruitment order as: large muscle fibres are being recruited during FES more often than during natural recruitment; the same muscle fibres are being recruited repeatedly as opposed to natural recruitment where alternating fibres are recruited to avoid fatigue and all recruited fibres are being activated synchronously rather than individually as observed during natural recruitment. Therefore, the use of FES can lead to an increased level of muscle fatigue compared to natural recruitment. This means that to maintain a constant muscle contraction when using FES for an extended period of time the stimulation charge must be increased.

1.5.1.1 Electrodes

FES can be delivered in three ways i) via electrodes placed on the skin (transcutaneous or surface stimulation), ii) via electrodes inserted through the skin (percutaneous stimulation) or iii) via electrodes implanted into the body and placed around or in close proximity to the nerve (implanted devices) [51]. Transcutaneous stimulation is simple and non-invasive, but it can be affected by poor selectivity of the correct muscle and can lead to skin irritation if improperly applied. Percutaneous stimulation allows for a greater selectivity of the correct motor unit. However, the needle electrodes used to deliver stimulation can be prone to failure, with Knutson *et al.* [56] reporting that in a study involving the insertion of 858 electrodes, 222 (26%) had to be removed due to failure. Implanted devices are designed for long term use, with their implantation involving an invasive and sometimes extensive surgical procedure. They apply stimulation via one of four types of electrode i) epimysial electrodes which are sutured directly onto the target muscles and are useful for the activation of thin muscles, ii) epineural electrodes which are sutured to tissue around the nerve and can be used to stimulate the nerve directly, iii) intraneural electrodes which penetrate into the nerve (currently only used in research applications) or iv) cuff electrodes which are placed directly around the nerve trunk and are the most common method of implanted stimulation. These implanted electrodes allow for more targeted stimulation than transcutaneous electrodes, with a much lower stimulation charge required to invoke a response. However, they create greater safety and biocompatibility issues, involve extensive surgery and are expensive.

There are two types of transcutaneous electrode configuration, monopolar and bipolar. In a bipolar electrode configuration the active electrode and reference electrode are situated close together, forming a small electrical circuit. In a monopolar configuration, the active electrode is positioned on top of the target nerve, with the reference electrode positioned somewhere along the neural pathway. While a bipolar configuration allows for targeting of specific motor units, monopolar configurations are popular when using electrode arrays, as only one reference electrode is required.

1.5.1.2 Stimulation Parameters

The stimulation parameters required to evoke an effective muscle contraction vary depending on the electrode type and target muscle. Each electrical stimulation pulse can be characterised by its pulsewidth, current, waveform and frequency.

Pulsewidth, also referred to as pulse duration, is the duration of each stimulation pulse and is normally in the range of 100 to 500 microseconds (μs). Stimulation current is the current applied during each stimulation pulse and for transcutaneous stimulation is normally in the range of 10 to 100 mA. The charge (Q) delivered during each electrical stimulation pulse is the stimulation current (I) multiplied by the pulsewidth (P), as shown in Equation 1.1, and is measured in Coulombs.

$$Q = I \times P \quad (1.1)$$

As can be seen in Equation 1.1, the charge delivered during each stimulation pulse can be increased by increasing the pulsewidth or the stimulation current. An increase in charge will lead to an increase in muscle fibre recruitment and result in a greater force being generated. The production of a greater force results in faster muscle fatigue, therefore it is important to only apply as much force as necessary to complete the desired task.

The waveform can either be biphasic, with a positive and negative charge, or monophasic, which applies only a positive or negative charge. A biphasic waveform is widely regarded as safer as the polarity of the charge entering the body is balanced. As such, for chronic applications electrical stimulation should always be charge balanced. This can be achieved through either: a monophasic charge balanced waveform, where a large short stimulating pulse (which activates the motor units) is followed by a longer period of small current in the opposing direction resulting in an overall neutral charge; or a biphasic waveform, where a stimulating current pulse in one direction is followed by a similar, charge balancing, pulse in the opposite direction. An example of these two waveforms is shown in Figure 1.9.

Stimulators are designed to work with either a fixed current or fixed voltage output, with the charge that is applied to the nerve depending on the impedance created by the contact with the skin. A voltage regulated stimulator applies a constant voltage (V) following the principles of Ohm's law, shown in Equation 1.2.

$$V = I \times R \quad (1.2)$$

As can be seen in Equation 1.2, when using a voltage regulated stimulator an increase in impedance (R) results in a decrease in the current (I) being delivered to the skin. A current regulated stimulator is not affected by a change in impedance. This results in a constant current being delivered to the skin, and in turn the nerve, generating a consistent muscle

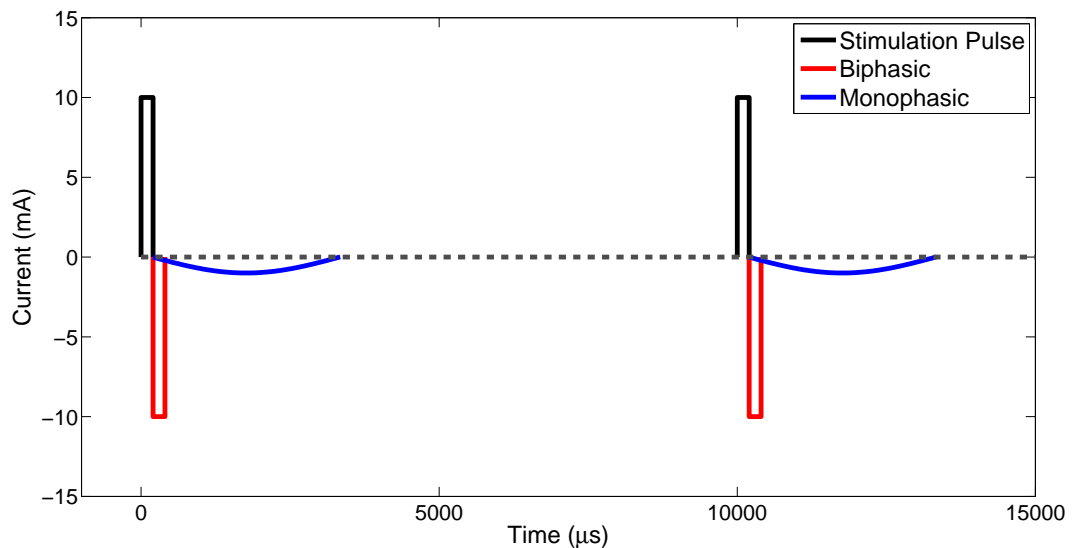


Figure 1.9: Example of electrical stimulation waveforms. A stimulating pulse (shown in black) is applied with a current amplitude of 10 mA, a pulsewidth of 200 μ s and a frequency of 100 Hz. This stimulating pulse is charge balanced by a biphasic pulse (shown in red) and a monophasic charge balanced pulse (shown in blue).

contraction. If the electrode becomes dislodged or damaged this current may be applied over a smaller surface area, resulting in an increase in the current density applied to the skin. In the most extreme case this could cause skin burns or tissue damage, however modern stimulators are designed to detect these situations and to limit the current accordingly. A voltage regulated stimulator does not allow control of the current being applied to the nerve, meaning that a consistent muscle contraction is not guaranteed. Therefore, when choosing between a current or voltage regulated stimulator a balance has to be struck between the risk of damage to the skin or tissue and the need for a consistent muscle contraction. While in a transcutaneous system voltage regulation will almost certainly prevent damage to the skin, with due vigilance current regulated stimulation can be used safely and achieve a far more consistent muscle contraction. Almost all implanted systems use current regulated stimulation as there is less variability in impedance, resulting in less chance of tissue damage, and a constant muscle contraction is of utmost importance.

Depending on stimulation frequency, electrical stimulation is capable of generating either a tetanic (constant) or twitch (intermittent) muscle contraction (see Section 1.3). To achieve a tetanic contraction the stimulation frequency must be greater than 12.5 Hz [51]. The greater the stimulation frequency above 12.5 Hz, the stronger the force generated. Due to an increase in the amount of time for which a fibre is recruited, increased stimulation frequency will result in faster muscle fatigue resulting in a decline in force.

FES has been used for a number of clinical applications. One of the most successful of these has been the use of FES to improve ambulation in patients who suffer from foot drop caused

by a stroke or SCI [57]. FES has also been used to stimulate i) the triceps to improve upper limb function [58, 59] ii) muscles of the upper leg as an exercise modality after stroke and SCI [60, 61], and iii) the sacral nerve roots to improve bladder and bowel function after SCI [62, 63]. In tetraplegic patients who lack the ability to breathe independently and are reliant on chronic mechanical ventilation FES has been applied to the phrenic nerve or diaphragm to generate an artificial breathing pattern, enhancing inhalation and enabling the removal of mechanical ventilation [64, 65, 66]. This thesis will focus on the use of FES of the abdominal muscles to improve respiration in tetraplegia.

1.5.2 Abdominal FES

FES has previously been used to activate the abdominal muscles. This has been achieved using: an implanted system to activate their thoracic nerve roots at the spinal cord [67, 68]; magnetic stimulation of these thoracic nerve roots [69] and the transcutaneous application of FES to the abdominal muscles, a technique called Abdominal Functional Electrical Stimulation (AFES). AFES is commonly applied to either, or both of, the rectus abdominis and external oblique muscle groups (see Section 1.4.1). It has been suggested that AFES training increases muscle mass, providing greater support to the abdominal contents. As the abdominal contents act as a pivot point for the diaphragm when it contracts, the greater support provided to them by the abdominal muscles places the diaphragm in a more efficient position after contraction [70]. It is also possible that by achieving an acute increase in respiratory function, AFES is assisting motor relearning, teaching the body a more efficient method of respiration. A typical electrode placement for a transcutaneous AFES system is shown in Figure 1.10.

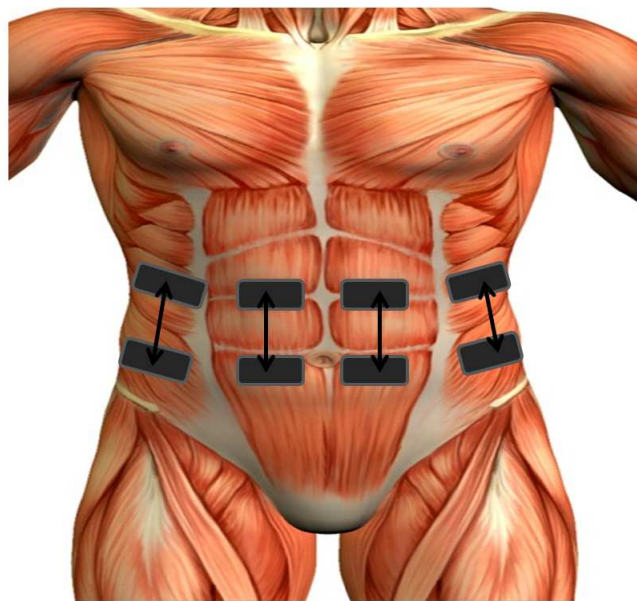


Figure 1.10: Electrode placement for abdominal stimulation showing four pairs of electrodes, positioned to stimulate the rectus abdominis and external oblique muscles on either side of the body.

As the abdominal muscles are an important muscle group for forced exhalation and cough, the strengthening of this muscle group can lead to an improvement in respiratory function. The application of AFES has been shown to achieve an acute increase in quiet breathing and cough function [71, 72]. The use of an AFES training program has also been shown to achieve longitudinal changes in quiet breathing and cough function [70, 73]. Despite these positive results AFES has yet to be introduced as a standard clinical treatment modality. This thesis will focus on the development of new technology and protocols to aid the clinical introduction of AFES with the tetraplegic population.

1.6 Aim and Objectives

The overall aim of this thesis is to add evidence to support the clinical introduction of AFES to improve the respiratory function of both acute ventilator dependent and sub-acute tetraplegic patients. This aim will be achieved by developing and implementing new technologies and protocols, which will firstly be tested with the able bodied population, and then developed for use with tetraplegic patients. The feasibility and effectiveness of these technologies and protocols to improve respiratory function will be investigated with acute ventilator dependent and sub-acute tetraplegic patients.

The objectives that will lead to the accomplishment of this aim are:

1. **Technological development** To develop technology capable of overcoming the challenges that exist in using AFES with the tetraplegic population. This new technology should include systems capable of synchronising AFES with the respiratory activity of both acute ventilator dependant and sub-acute tetraplegics and a system that can be used to identify the motor points of the abdominal muscles. The integration of AFES with existing methods for improving the cough of sub-acute tetraplegic patients will also be addressed.
2. **Clinical evaluation** To evaluate and develop the optimum protocols for the use of AFES with the tetraplegic population. Clinical studies will be undertaken to establish whether the use of novel protocols, which incorporate the new technology developed in objective 1, are feasible, and whether they can be used to improve respiratory function. An investigation into the optimum duration of an AFES training program will also be undertaken.

1.6.1 Thesis Outline

These aims will be addressed in the chapters of this thesis, which are outlined below.

Chapter 2 : A review of studies investigating the effect of paralysis on respiration in tetraplegia is provided in this chapter. Various methods that have been employed to help improve the respiratory function of people with tetraplegia are reviewed, with a particular focus on AFES. The open questions surrounding the use of this technique, and possible

developments that should improve this techniques effectiveness, are presented here.

Chapter 3 : The experimental methods used throughout this thesis are presented here. This includes a description of the methods used to measure respiratory function, the methods used to record respiratory activity and a description of the AFES system. An overview of the statistical methods used in this thesis is also given. This chapter also includes a small study investigating the optimum set up parameters for using a respiratory effort belt to measure respiratory function.

Chapter 4 : In this chapter the use of non-intrusive sensors for the real-time detection and classification of respiratory activity is explored. A range of non-intrusive sensors are evaluated to assess their suitability for real-time detection of respiratory activity. The non-intrusive sensors found to be capable of real-time detection of respiratory activity are then used to develop a statistical classification algorithm to classify respiratory activity, capable of differentiating between a cough and quiet breath in real-time.

Chapter 5 : A novel application of NMES to locate the position of the motor points of the abdominal muscles is presented here. The feasibility of using this technique for abdominal muscle motor point detection is demonstrated with 10 able bodied and five tetraplegic participants. The repeatability and uniformity of these motor point positions is evaluated and compared for both groups, with the implications of these results discussed. The repeatability of this technique is demonstrated and the potential of this technique to improve the effectiveness of AFES research is discussed.

Chapter 6 : This chapter begins by documenting a single participant case study, used to demonstrate the feasibility of using AFES to assist ventilator weaning for the tetraplegic population who retain some diaphragm function. A larger feasibility study investigating the use of AFES to improve the respiratory function of acute ventilator dependant tetraplegics and assist weaning from mechanical ventilation is then presented. This is the main clinical study conducted for this thesis. The engineering methods developed to allow the automatic synchronisation of AFES with mechanical ventilation or the participant's respiratory activity are described. The improvements in respiratory function gained during the eight week study are presented, along with the weaning outcomes for all participants and their matched controls. The potential future applications and implications of this new technique are also discussed.

Chapter 7 : A randomised crossover study investigating the effect of AFES training on respiratory function is described here. The feasibility of using five times weekly AFES training sessions for a period of eight weeks is demonstrated with three tetraplegic participants. The results achieved during the intervention and a four week control period are presented and discussed. A novel method of combining AFES with mechanical insufflation-exsufflation to

improve cough is also described.

Chapter 8 : This chapter draws on all the work presented in this thesis to provide a balanced assessment of the use of AFES to improve the respiratory function of people with tetraplegia. The limitations of AFES, along with the potential future work generated by the research presented here, are also discussed in this chapter.

Chapter 9 : The main conclusions of this thesis are summarised.

Chapter 2

Literature Review

“One never notices what has been done; one can only see what remains to be done.”

Marie Curie

2.1 Summary

Paralysis, or severe impairment, of the respiratory muscles causes many people with tetraplegia to have reduced respiratory function. Associated respiratory complications are a leading cause of morbidity and mortality for the tetraplegic population. This literature review begins by describing research conducted into the effect of tetraplegia on respiratory function. A number of techniques are available to improve the respiratory function of people with tetraplegia. None of these techniques are without drawbacks. The function, benefits and practicality of each system is discussed in detail, with a specific focus on abdominal functional electrical stimulation.

2.2 Respiratory Function in Tetraplegia

An injury to the cervical region of the spinal cord, termed tetraplegia, leads to paralysis, or severe impairment, of the abdominal and intercostal muscles, as well as paralysis or reduced function of the diaphragm. As these are the main muscles used for respiration, people with tetraplegia often have reduced respiratory function and an inability to generate an effective cough.

A number of studies have compared the predicted values of respiratory function for the able bodied population (see Section 1.4.2) with the respiratory function of people with tetraplegia. A summary of the results from a selection of these studies is shown in Table 2.1.

Table 2.1: Summary of studies investigating respiratory function in tetraplegia. The Forced Vital Capacity (FVC), Forced Exhaled Volume in one second (FEV_1), Peak Expiratory Flow (PEF), Tidal Volume (V_T), Maximum Inspiratory Pressure (MIP) and Maximum Expiratory Pressure (MEP) of people with tetraplegia, compared to the predicted value for the able bodied population, is shown. The injury levels of the participants and the minimum time post injury is also shown.

Author	Injury Level	Time Post Injury	FVC	FEV_1	PEF	V_T	MIP	MEP
Spungen <i>et al.</i> [36]	Tetra	> 2 years	52%	52%	-	74%	65%	36%
Langbein <i>et al.</i> [71]	C5-C7	> 1 year	64%	67%	60%	-	-	-
Linn <i>et al.</i> [74]	C2-C5	> 1 year	49%	52%	42%	-	-	-
	C6-C8	> 1 year	62%	69%	54%	-	-	-
Baydur <i>et al.</i> [75]	C3-C8	> 8 months	57%	65%	-	-	-	-
Thomaz <i>et al.</i> [76]	C4-C8	> 2 months	55%	-	-	-	-	-
Linn <i>et al.</i> [77]	C3-C5	> 1 year	49%	-	-	-	-	-
	C6-C8	> 1 year	73%	-	-	-	-	-

It should be noted that the studies presented in Table 2.1 did not exclude tetraplegic patients who had Lower Motor Neuron (LMN) damage. As intact LMNs are necessary for Functional Electrical Stimulation (FES) to be successful, some of the candidates in these

studies may not have been eligible for the Abdominal Functional Electrical Stimulation (AFES) studies conducted in this thesis. Patients with LMN damage will have flaccid paralysis, meaning that disuse atrophy occurs quickly after injury (see Section 1.3 for further details regarding LMN damage). As a result, these patients may display different levels of respiratory function compared to those without LMN damage, with the possibility that due to severe muscle atrophy the respiratory muscles, and hence respiratory function, are more severely compromised in these patients. Therefore, caution should be exercised when making a quantitative comparison of the respiratory function of participants in AFES studies with studies investigating the respiratory function of the general tetraplegic population, such as those detailed in Table 2.1. Within this thesis, the results of the studies presented in Table 2.1 will be used to provide a qualitative indication of the effect of tetraplegia on respiratory function.

As can be seen from Table 2.1 tetraplegia reduces respiratory function to a level well below the predicted values for the able bodied population, with this reduction in function shown to increase with ascending injury level [74, 77]. This reduced respiratory function has a direct impact on the ability of people with tetraplegia to generate an effective cough, leading to an inability to effectively clear the airway of secretions. This poor secretion clearance is a key factor in respiratory complications being a leading cause of morbidity and mortality for this population [2, 28, 29, 30] with a mortality rate of 21 percent [78].

Fishburn *et al.* [79] found that of 30 tetraplegic patients studied in the first 30 days post injury, 17 (57%) developed atelectasis or pneumonia. In a study investigating the number of respiratory complications observed in 261 tetraplegic patients in the first six weeks after injury Jackson and Groomes [80] found that 175 of the 261 (67%) participants developed a respiratory complication, with atelectasis (36%) and pneumonia (31%) the most common. These cases of atelectasis and pneumonia were found to occur on average 18 and 25 days post injury. This shows that respiratory complications are a common occurrence in the acute stage of injury. An early intervention which acts to improve respiratory function is likely to be beneficial in preventing respiratory complications in this patient group.

2.3 Clinical Methods to Support Respiration

A number of methods are currently employed in the clinical setting to compensate for the reduction in respiratory function caused by tetraplegia. For tetraplegic patients who are unable to breathe independently mechanical ventilation is used to provide artificial respiration. For people with tetraplegia who are unable to generate an effective cough, manually assisted coughing, mechanical insufflation-exsufflation and tracheal suctioning are all used to aid secretion removal.

2.3.1 Mechanical Ventilation

Respiratory failure leads to some patients with tetraplegia requiring mechanical ventilation in the acute stage of injury. This respiratory failure is commonly caused by paralysis or severe impairment of the respiratory muscles, the neurological level of Spinal Cord Injury (SCI) ascending one or two levels because of bleeding or swelling in the area of the trauma (reducing function of respiratory muscles not originally affected by the SCI) and subsequent respiratory complications [47]. Gay [81] reports that of the 12,000 new cases of SCI per year in the United States of America (USA), more than 2,700 lead to the patient requiring mechanical ventilation. Claxton *et al.* [82] reported that of 72 patients with tetraplegia, 29 (40%) required mechanical ventilation due to respiratory failure. Twenty six (90%) of these cases of ventilation occurred less than four days post injury, indicating that respiratory failure primarily occurs soon after injury.

For tetraplegic patients who require mechanical ventilation in the acute stage of injury the paralysis of the intercostal muscles becomes spastic over time, resulting in the chest wall becoming more rigid and no longer collapsing during inspiration [47]. Vital Capacity (V_C) has also been reported to improve significantly in the weeks following injury [83]. These two factors combine to mean that many of these patients will wean from mechanical ventilation. Gay states that of the 2,700 SCI patients who require mechanical ventilation annually in the USA, 2,000 will wean from mechanical ventilation and 500 will become ventilator dependant (with the other 200 patients dying in the acute stage of injury) [81]. The duration of mechanical ventilation varies significantly between patients, with no clearly defined prediction methods. Claxton *et al.* [82] found that patients required mechanical ventilation for an average duration of 11 ± 31 days, showing a wide range of ventilation durations. Current understanding is that injury level, age and sex may be the best indicators of this ventilation duration [39, 38, 42]. Therefore, while many people with tetraplegia will require ventilation in the acute stage after injury the majority of these patients will wean from ventilation. However, there is a wide variation in the duration of ventilation, with this duration not easy to predict.

Mechanical ventilation is associated with an increase in the likelihood of developing a respiratory infection [84], with Krause *et al.* [85] reporting that the mortality rate for people with an SCI was approximately three and a half times greater if they required mechanical ventilation. The need for ventilation also reduces a persons quality of life, can delay rehabilitation [27] and leads to an increased cost for the health care provider of approximately £1000 per ventilated day [46].

Several methods are used to promote weaning from mechanical ventilation. Intermittent Mandatory Ventilation (IMV) involves the degree of ventilatory support being decreased over time until the patient is eventually disconnected from the ventilator and required to

breathe independently. Spontaneous Breathing Trials (SBTs) (often referred to as t-piecing due to the use of a t-piece to provide oxygen) encourage the patient to breathe on their own several times a day. The duration of initial SBTs will be short due to the patient suffering respiratory muscle fatigue. As the respiratory muscles regain strength the duration of each SBT is increased until the patient no longer requires the support of mechanical ventilation [86]. When using IMV there is no clear point at which to remove mechanical ventilation. This results in SBTs freeing a patient from ventilation up to three times faster than IMV [84]. The addition of an intervention to strengthen the abdominal muscles during the weaning process may lead to an improvement in respiratory function and result in a reduced time to wean.

An improvement in respiratory function resulting in earlier weaning from, or avoidance of, mechanical ventilation will i) improve the patient's quality of life ii) allow the patient to begin rehabilitation earlier iii) reduce the likelihood of the patient developing respiratory complications and iv) result in a significant cost saving for the local health care provider.

To evaluate the effectiveness of an intervention in enabling faster weaning from mechanical ventilation it is necessary to clarify when a person has successfully weaned. Narh *et al.* [38] suggest that someone has weaned from mechanical ventilation after seven days without ventilatory support. Within the Queen Elizabeth National Spinal Injuries Unit it has been observed that most people who achieve a period of 24 hours without ventilatory support will require no further mechanical ventilation, with the exception being people who suffer from comorbidities such as respiratory complications. Twenty four hours of ventilator free breathing was also used by Martin *et al.* [87] to define successful weaning. Therefore, by comparing the time to achieve both 24 hours and seven days without ventilatory support for patients who receive an intervention with a control group, matched with each patient based on injury level, age and sex, it should be possible to assess the effectiveness of an intervention in enabling faster weaning from ventilation.

2.3.2 Assisted Secretion Removal

In the clinical setting antibiotics, mucolytics (medicines that make mucus less sticky and easier to cough up) and the application of number of drugs via a nebuliser are all used to break up secretions and assist secretion removal. Another approach to assist secretion removal for tetraplegic patients is to apply a manual intervention. Currently manually assisted coughing, mechanical insufflation-exsufflation or, in the case when a tracheostomy is present, tracheal suctioning, are commonly used to aid secretion removal in the clinical setting.

2.3.2.1 Manually Assisted Coughing

Manually assisted coughing involves the manual compression of the thoracoabdominal cavity during the exhalation phase of a voluntary cough. Various studies have shown that this compression increases Cough Peak Flow (CPF) and Maximum Expiratory Pressure (MEP)

compared to a voluntary cough [88, 89, 90], helping to release secretions trapped in the airway. While a manually assisted cough is a safe and effective procedure for secretion removal it needs to be provided by a trained caregiver. This has associated cost and resource implications for the local health care provider [91, 92]. Additionally, the force used by the caregiver to generate an effective cough is subjective. This makes it unlikely that the same force is applied by different caregivers, or by the same caregiver in consecutive sessions, resulting in a variability in the effectiveness of the technique.

2.3.2.2 Tracheal Suctioning

For many people with acute tetraplegia a tracheostomy, which is an incision in the trachea to provide direct access to the airway, is applied. This allows a tube providing suction to be inserted into the tracheostomy tube to remove secretions from the airway, a technique known as tracheal suctioning. While tracheal suctioning can be used to successfully remove secretions, it is uncomfortable for the patient and can induce gagging. Additionally, tracheal suctioning often misses the left bronchus, which Sancho *et al.* [93] state is one of the contributing factors to 80 percent of pneumonia occurring in the left lung of the SCI population. Moreover, tracheal suctioning can lead to serious complications including hypoxemia, bronchoconstriction and cardiac arrhythmias [93].

2.3.2.3 Mechanical Insufflation-Exsufflation

An alternative method to help clear secretions and improve respiration is Mechanical Insufflation-Exsufflation (MI-E). MI-E involves applying alternating positive and negative pressure to the user's airway to simulate a cough. A number of studies have shown that MI-E is more effective at removing secretions and reducing respiratory infections than both manually assisted coughing and tracheal suctioning [92, 93, 94], with the advantage over the latter that secretions are removed from both bronchi. MI-E has also been shown to significantly reduce the length of stay in an intensive care unit and reduce the rates of reintubation [95], with users finding MI-E to be more comfortable than tracheal suctioning [93, 96].

All of the above outlined techniques can successfully be used to aid secretion removal in the clinical setting, and hence reduce the risk of respiratory infection. However, all of these techniques are passive and are used to replace the user's own cough, leading to none of the techniques directly improving respiratory function. An alternative solution, which uses training of the respiratory muscles to provide an improvement in respiratory function, may be beneficial to a patient's long term respiratory health. This thesis will focus on the use of electrical muscle stimulation to improve respiratory function.

2.4 Methods to Improve Respiratory Function

During respiration the diaphragm is the main muscle used for inspiration, the intercostal muscles are active during both inspiration and expiration and the abdominal muscles are the main muscle group used during a forced exhalation, such as that taken during exercise or cough. A number of methods have been developed to improve the respiratory function of people with tetraplegia, with these methods designed to improve the function of one or several of these major respiratory muscles. The methods that have been used include electrical and magnetic stimulation and respiratory muscle training, with each of these methods being discussed in detail in this section.

Electrical stimulation involves the application of a train of electrical pulses to a motor nerve, causing the associated muscle to contract (see Section 1.5 for further explanation). An improvement in respiratory function has been achieved by applying electrical stimulation to either the diaphragm or the intercostal or abdominal muscles of tetraplegic patients.

Magnetic stimulation can be used to produce an electrical field in neural tissue. If this electric field is large enough it can generate enough current to depolarise a nerve, creating an action potential and resulting in a contraction of the associated muscle. Magnetic stimulation has been used to improve respiratory function in tetraplegia in two ways: i) by activating the phrenic nerve to cause a contraction of the diaphragm and ii) by activating the thoracoabdominal nerve roots, causing the abdominal muscles to contract. While magnetic stimulation to activate the diaphragm or abdominal muscles has the advantage over transcutaneous electrical stimulation of being painless, as the cutaneous pain receptors are not activated, it is associated with some problems of practicality. Firstly, magnetic stimulation systems use a large stimulation coil that requires a large amount of power. This requires these systems to be mains powered, making them non-portable and reducing their practicality in a clinical setting. The amount of power that can be generated is also limited by how fast the capacitors used to deliver the magnetic stimulation can be charged. Finally, the magnetic coil used to deliver stimulation can generate a large amount of heat, creating a potential risk of skin burns to the user. Despite these drawbacks, several studies have demonstrated the use of magnetic stimulation to improve respiratory function.

Respiratory Muscle Training (RMT) uses flow resistive devices, pressure threshold devices or abdominal weights to train either the inspiratory or expiratory muscles. RMT has been used with the tetraplegic population to improve respiratory function by training both the inspiratory (intercostal and diaphragm) and expiratory (abdominal) muscles.

Studies that have applied electrical or magnetic stimulation or respiratory muscle training to the diaphragm, intercostal or abdominal muscles will be discussed in the remaining portion of this chapter.

2.4.1 Diaphragm

The phrenic nerve is used to send signals from the brain to the diaphragm, the main respiratory muscle used during inhalation. This nerve originates from C3 to C5 of the spinal cord. Therefore, anyone with an SCI with a neurological level of injury of C5 or above is likely to have impaired diaphragm function, while an SCI with a neurological level of C2 or above is likely to result in complete paralysis of the diaphragm. For some people with a complete SCI in the range C3 to C5 who have severely impaired diaphragm function, and almost all people with a complete SCI at level C2 or above, respiratory support in the form of mechanical ventilation is required. For these patients stimulation of the phrenic nerve can be used to make the diaphragm contract, even when paralysed. This contraction causes the diaphragm to descend, decreasing intrathoracic pressure and resulting in an inhalation. When stimulation is stopped the diaphragm relaxes and returns to its original position, increasing intrathoracic pressure and causing an exhalation. Repeated rhythmical stimulation of the phrenic nerve can be used to create an artificial breathing pattern and reduce the need for mechanical ventilation, a technique called diaphragm pacing. For diaphragm pacing to be successful the phrenic nerve must be intact [34]. As the phrenic nerve originates from C3 to C5 of the spinal cord, it is common that after a cervical SCI with a neurological level of C5 and above the patient will have sustained LMN damage to the phrenic nerve. This means that the phrenic nerve cannot be stimulated [97].

Previous studies have used both electrical or magnetic stimulation of the phrenic nerve to achieve diaphragm pacing with tetraplegic participants who did not have LMN damage.

2.4.1.1 Electrical Diaphragm Pacing

Electrical stimulation of the phrenic nerve for diaphragm pacing is currently achieved by either phrenic nerve or intramuscular diaphragm pacing. It should also be noted that transcutaneous electrical stimulation can be used to activate the phrenic nerve. While this can be useful for identifying whether the phrenic nerve remains intact, necessary for a patient to be a suitable candidate for diaphragm pacing (see Section 2.4.1.2 for more information on this technique), due to co-activation of muscles in the neck transcutaneous electrical stimulation is not suitable for long term electrical diaphragm pacing.

Phrenic Nerve Pacing Phrenic Nerve Pacing (PNP)¹ is a technique where electrodes are implanted around the phrenic nerves that control each hemidiaphragm. To trigger stimulation a signal is sent from a transmitter, located outside the body, to an implanted radio frequency receiver. The receiver then sends a signal to the electrodes that electrically stimulate the phrenic nerves, causing the diaphragm to contract.

In 1968 Judson and Glenn [98] published a single participant case study where PNP was

¹PNP is sometimes referred to in the literature as phrenic nerve stimulation

successfully used to aid a patient with primary hypoventilation, preventing them from requiring mechanical ventilation. In 1972 Glenn and colleagues [99] published the first use of PNP to aid people with SCI. In this study PNP was used with a C1/2 tetraplegic patient to replace the need for mechanical ventilation. This was followed in 1976 by the first large scale documentation of the use of PNP to decrease reliance on mechanical ventilation for people with SCI [64]. In the proceeding years, the use of PNP to replace mechanical ventilation for people with SCI has grown, with the technique being applied to over 2,400 patients worldwide by 2013 [100].

PNP has some major advantages over mechanical ventilation. Successful diaphragm pacing results in decreased dependance on mechanical ventilation, which reduces the risk of developing respiratory infections associated with being connected to a mechanical ventilator [74]. PNP users also have increased mobility as they are not attached to a mechanical ventilator [34], and as such, no longer have the fear associated with being disconnected from the ventilator [97]. Users are also less likely to suffer social stigma, have improved speech, have reduced reliance on care giver support and have a greater level of overall health compared to using mechanical ventilation [101, 102]. These factors all combine to improve the user's quality of life.

PNP is not a panacea and has some significant drawbacks. Firstly, the use of PNP cannot achieve instant full time ventilatory support. For PNP candidates, it is likely that the diaphragm will have suffered from disuse atrophy during the period after SCI. For PNP to be successful, a reconditioning period, aimed at strengthening the diaphragm, must be conducted. Glenn *et al.* [103] report that for four adults (age 15 to 26 years) the length of this reconditioning period was three to four months. Furthermore, the implantation of the PNP system is most commonly performed through an incision in the chest, known as a thoracotomy. This is a major surgical procedure and is associated with a lengthy hospital stay and high costs [34, 51]. As the technique for implanting the electrodes requires manipulation of the phrenic nerve, this can also lead to additional phrenic nerve damage [64]. PNP was also associated with a high infection and failure rate in early studies, although Sheffler and Chae report that the infection and failure rates associated with PNP have significantly improved [51]. Even with this improvement in failure rate, the risk of device failure means that a ventilator is required to be on stand by while PNP is in use [81]. Therefore, while PNP is an effective technique to support inspiration, with advantages over mechanical ventilation such as reduced respiratory infection rates and improved quality of life, a less invasive and less costly alternative would be beneficial for both the patient and the local health care provider.

Intramuscular Diaphragm Pacing Diaphragm pacing can also be achieved by electrically stimulating the phrenic nerve at the location where it enters each hemidiaphragm, a technique called intramuscular diaphragm pacing (DP). To stimulate the phrenic nerves, electrodes are implanted onto the diaphragm at the motor points of the phrenic nerves, via a

small incision in the abdomen, known as a laparoscopy [65]. The phrenic nerves can then be stimulated rhythmically, causing the diaphragm to contract and achieving diaphragm pacing. By 2012, 350 patients worldwide had been fitted with a DP system [66]. Tedde *et al.* [104] reported that six months after implantation, 60 percent (3 of 5) of patients fitted with a DP system were able to breathe independently of mechanical ventilation, relying solely on DP. This correlates with the findings of Onders *et al.* [105] who report that greater than 70 percent of people who were fitted with DP systems were able to permanently free themselves from mechanical ventilation. As with PNP, this reduced dependence on mechanical ventilation reduces the risk of respiratory infection associated with being connected to mechanical ventilation.

The implantation of a DP system has an advantage over PNP in that a laparoscopy is not a major surgical procedure, with a shorter hospital stay and lower overall cost than a thoracotomy [106]. Although the risks of a laparoscopy are lower than that of a thoracotomy, the procedure is not without risk. There is a small risk of the patient developing a pneumothorax or subcutaneous emphysema caused by the placing of the electrodes [106]. The system developed by DiMarco *et al.* [65] also has wires exiting the skin to an external power source. These wires pose a risk of infection or breakage, which would require another laparoscopy to correct. While DP has been shown to be capable of generating a similar Tidal Volume (V_T) to that achieved using PNP [106] it is not an instant solution, with users required to undergo a reconditioning program to strengthen the diaphragm, avoid fatigue and maintain adequate ventilation. Onders *et al.* [66] report that the reconditioning time that allowed participants to achieve four hours of DP breathing was less than one week for 18 to 20 year olds who had been on a ventilator for less than one year. However, for two participants over 65 years of age the reconditioning time required to achieve four hours of DP breathing was 21 weeks. Despite these drawbacks DP is a viable alternative to mechanical ventilation, with benefits over PNP of reduced cost and reduced length of hospital stay.

2.4.1.2 Magnetic Diaphragm Pacing

Man *et al.* [107] describe three methods of using magnetic stimulation of the phrenic nerve to achieve diaphragm pacing. When a patient is sitting upright magnetic stimulation can be applied to the back of the neck at level C7, a technique called cervical magnetic stimulation. This technique achieves diaphragm pacing by stimulating the phrenic nerves roots, causing a contraction of the diaphragm. Anterior pre-sternal magnetic stimulation involves placing the patient in a supine position and applying stimulation over the sternum. This activates the phrenic nerve at the point where it enters the diaphragm, again causing a contraction of the diaphragm and achieving diaphragm pacing. Unilateral/bilateral anterolateral stimulation can also be used to stimulate the phrenic nerve. In this case stimulation is applied on either one (unilateral) or both sides of the neck (bilateral) to achieve phrenic nerve stimulation at the nerve root.

While the use of magnetic stimulation for diaphragm pacing has the advantage over electrical diaphragm pacing (see Section 2.4.1.1) of being non-invasive, there are two significant drawbacks when using the technique with people with tetraplegia. Firstly, for both cervical and unilateral/bilateral anterolateral magnetic stimulation, stimulation is applied at the cervical level and requires the users neck to be moved to allow placement of the stimulation coil. Polkey *et al.* [108] state that this would make magnetic stimulation unsuitable for anyone with an unstable SCI, common in the acute stage of injury. Secondly, while anterior pre-sternal magnetic stimulation does not require neck movement, there is only limited data supporting the use of this technique [107].

One potential use of magnetic stimulation of the phrenic nerve is to identify candidates who have not suffered LMN and who would be suitable candidates for electrical diaphragm pacing. To achieve this, magnetic stimulation is applied to the motor cortex, the area of the brain responsible for motor function, and the results compared to those achieved using cervical magnetic stimulation. If there is no response of the diaphragm to stimulation of the cortex (indicating diaphragm paralysis) and the diaphragm contracts using cervical magnetic stimulation (indicating that the phrenic nerve is intact) then the patient is likely to be a suitable candidate for electrical diaphragm pacing [109]. It should be noted that transcutaneous electrical stimulation can also be applied to the same areas to identify candidates who have not suffered LMN. However, due to electrical stimulation activating cutaneous pain receptors, this method is likely to be more painful for the user than magnetic stimulation.

In summary, for people with tetraplegia whose diaphragm function renders them unable to breathe spontaneously, PNP, DP and magnetic diaphragm stimulation can be used to activate the diaphragm and create an artificial breathing pattern, termed diaphragm pacing. Successful diaphragm pacing results in decreased dependence on mechanical ventilation and reduced risk of respiratory infection. As the diaphragm is only active during inhalation (see Section 1.4.1 for more information on respiratory muscle function) diaphragm pacing does not improve expiratory function. The expiratory muscles are used to generate a cough, the body's main defence against respiratory infection. Therefore, a gain in expiratory muscle function that leads to the generation of a more effective cough should decrease the risk of respiratory infection and subsequent respiratory complications such as pneumonia and atelectasis.

2.4.2 Intercostal Muscles

The intercostal muscles are innervated by 24 separate nerves, termed the intercostal nerves, which originate from the spinal cord at T1 to T11. Each of these nerves innervates muscles that have both an inspiratory and expiratory function. The intercostal muscles play a significant role in inhalation, being responsible for approximately 35 percent of a persons V_C [34]. They also play a role during forced exhalation, such as that taken during a cough. Both electrical stimulation and RMT techniques have been applied to the intercostal muscles

to try and improve respiratory function.

2.4.2.1 Intercostal Spinal Cord Stimulation

Spinal Cord Stimulation (SCS) is the electrical stimulation of spinal nerve roots via an epidural electrode placed on the spinal cord. DiMarco *et al.* [110] used SCS of the intercostal nerve roots (located at T1 to T4) to activate the intercostal muscles, denoted Intercostal Spinal Cord Stimulation (iSCS), of five ventilator dependent tetraplegic patients. They found that initially iSCS provided very small (less than 240 mL) inspired volumes. After a reconditioning program participants were able to achieve inspired volumes of as large as 850 mL. However, due to co-activation this reconditioning program led to hypertrophy of the upper trunk muscles, which is undesirable. DiMarco *et al.* [111] have also combined iSCS with DP and found that it could be used to achieve extended periods (between 16 and 24 hours per day) of ventilator free breathing. Both these forms of electrical intercostal muscle stimulation require a surgical technique to implant electrodes on the spinal cord.

Due to the intercostal muscles being innervated by nerves that have both an inspiratory and expiratory function, transcutaneous electrical stimulation of the intercostal muscles would cause contraction of muscles that had both an inspiratory and expiratory role. This makes non-invasive transcutaneous electrical stimulation an unsuitable method to achieve intercostal muscle stimulation. Due to a lack of data on the effectiveness of intercostal muscle stimulation, and an inability to apply this technique non-invasively, it remains experimental [112].

2.4.2.2 Intercostal Muscle Training

Liaw *et al.* [113] used RMT to train the inspiratory muscles (primarily the diaphragm and intercostal muscles) of 10 tetraplegic (C4 to C7) participants who were less than six months post injury, comparing changes in respiratory function to 10 tetraplegic controls. Intervention participants were asked to inhale against a resistive load for up to 20 minutes, twice per day, seven days a week, for six weeks. They found a statistically significant increase in Forced Vital Capacity (FVC), which is a measure of inspiratory muscle function (see Section 1.4.2), for both groups. They also found a statistically significant increase in Forced Exhaled Volume in one second (FEV_1), Maximum Inspiratory Pressure (MIP) and MEP over the six week period for both groups and a statistically significant increase in Peak Expiratory Flow (PEF) for the intervention group. Notably the FVC, FEV_1 and PEF of the treatment group increased by 67, 63 and 39 percent compared to a 27, 21 and 23 percent increase for the control group. It should be noted that all measures of respiratory function were greater for the control group both pre and post intervention. In summary, this study appears to show an improvement in respiratory muscle function using inspiratory muscle training of the intercostal muscles.

Martin *et al.* [87] applied inspiratory muscle training, using a pressure threshold device, to assist weaning from mechanical ventilation for 10 critically ill able bodied participants.

Participants were required to generate an inspiratory pressure greater than a threshold to open a valve and obtain a breath. They found an increase in MIP from 8 ± 3 cmH₂O to 18 ± 7 cmH₂O. They also found that nine of the 10 (90%) participants weaned from mechanical ventilation. No further respiratory measures were presented, making it difficult to assess the effectiveness of RMT in this study.

Interestingly both Liaw *et al.* [113], who applied inspiratory muscle training, and Zupan *et al.* [114], who applied expiratory muscle training (see Section 2.4.3.1), found a decrease in dyspnea (shortness of breath) after RMT. Despite this, Houtte *et al.* [115] state that the lack of controlled studies make it difficult to draw conclusions on the effectiveness of RMT to improve the respiratory function of people with tetraplegia. They state that it is difficult to differentiate between the effect of the intervention and natural recovery in many of these studies, a problem inherent in many studies with the SCI population. This corroborates the opinions of Stiller and Huff [116] who suggest that the lack of controlled RMT studies make it difficult to exclude natural recovery to explain improvements in respiratory function. Due to the lack of certainty regarding the effectiveness of the intervention, RMT is currently not an established method for improving the respiratory function of the tetraplegic population.

2.4.3 Abdominal Muscles

The abdominal muscles are innervated by the thoracoabdominal nerves, which originate from the spinal cord at T7 to T11. They are the major muscle used for forced exhalation, such as that taking during coughing and exercise. An improvement in abdominal muscle function will result in improved cough generation, which should lead to more effective secretion clearance and decrease the risk of developing a respiratory infection. RMT, magnetic stimulation and electrical stimulation have all been applied to the abdominal muscles to improve respiratory function.

2.4.3.1 Abdominal Muscle Training

Zupan *et al.* [114] investigated the effect of inspiratory and expiratory muscle training on the respiratory function of 13 people with tetraplegia (C4 to C7). Inspiratory muscle training was performed using breathing exercises that recruit inspiratory muscles, principally the diaphragm and intercostal muscles. Expiratory muscle training was performed using breathing exercises that recruit the abdominal muscles and was coupled with AFES (see Section 1.5.2 and 2.4.4). Each method was performed for up to 30 minutes, twice per day, six days a week, over two four week periods. They found that when measuring the patient's unassisted effort, inspiratory muscle training caused a larger increase in respiratory function than expiratory muscle training. Inspiratory muscle training was found to increase FVC and FEV₁ by 19 and 20.5 percent in the sitting position and 17.5 and 16 percent in the supine position, while expiratory muscle training was found to cause no significant increase in FVC and FEV₁ in the sitting position and a 17 and 16 percent increase in the supine

position. When measuring respiratory function with the support of AFES, FVC and FEV₁ were greater than the participant's unassisted efforts. These results should be treated with caution as the addition of AFES during expiratory muscle training may effect the expiratory muscle training results, as AFES training alone has been shown to lead to an improvement in FVC and FEV₁ (see Section 2.4.4).

2.4.3.2 Magnetic Abdominal Stimulation

Magnetic stimulation can also be used to activate the abdominal muscles by applying a magnetic field close to the thoracic spinal cord. This magnetic field stimulates the thoracoabdominal nerve roots (located at T7 to T11), causing the abdominal muscles to contract. As the nerve roots below the level of SCI usually remain intact, this is a viable method for improving the respiratory function of people with a cervical, or high thoracic, SCI [69].

Lin *et al.* [69] used magnetic stimulation to activate the thoracoabdominal nerve roots of 13 tetraplegic patients (injury levels C4 to C7). They showed that the MEP generated using magnetic stimulation was increased compared to voluntary efforts. They also found that the respiratory flow rates of the tetraplegic participants, generated using magnetic stimulation, were comparable to the voluntary respiratory flow rates generated by able bodied individuals. The improvements in MEP and respiratory flow rates achieved using magnetic stimulation were not found to be statistically significantly different to the results achieved during the maximum spontaneous efforts of the participants. Polkey *et al.* [108] found that magnetic stimulation could be used to generate large pressures in able bodied participants, although no comparison of the pressure or respiratory flow rates that could be achieved with and without stimulation were made. These results suggest that magnetic stimulation can be used to improve cough generation.

Lin *et al.* [69] found that at high stimulation intensities respiratory function actually decreased. This was believed to be caused by the recruitment of inspiratory antagonists, attributed to the poor targeting of muscles with magnetic stimulation. Polkey *et al.* [108] also found a high variability in the respiratory flow rate that could be generated using magnetic stimulation, which they hypothesis to be due to glottal closure. DiMarco [34] alludes to these drawbacks of magnetic stimulation. However, he is of the belief that with further development of the equipment and identification of the correct users, magnetic stimulation could become a practical tool to improve respiratory function.

2.4.3.3 Abdominal Spinal Cord Stimulation

Spinal Cord Stimulation (SCS) can also be used to activate the abdominal muscles, denoted Abdominal Spinal Cord Stimulation (aSCS). In an aSCS system three electrodes are implanted directly into the spinal cord, around the lower thoracoabdominal and upper lumbar

nerve roots (T9, T11 and L1). These electrodes can be activated using the signal from an external transmitter, controlled by the user or their caregiver.

The use of aSCS to improve respiratory function was first documented by DiMarco *et al.* [117]. In this preliminary study, aSCS was used with one tetraplegic patient (C5/6) who had difficulty clearing secretions. This study found that the combined activation of the electrodes implanted at T9 and L1, compared to activation of each electrode individually, improved PEF (7.4 L/s v 6.4 and 5.0 L/s) and MEP (132 cmH₂O v 90 and 82 cmH₂O), although no baseline measures of respiratory function were reported. In 2009 DiMarco *et al.* [67, 68] presented a follow-up study where aSCS was used with a further nine tetraplegic patients to achieve a mean CPF of 8.6 ± 1.8 L/s and a mean MEP of 137 ± 30 cmH₂O, both of which approach the predicted values for the able bodied population. Interestingly, as with the results reported in [117], these values were achieved by stimulating the electrodes implanted at T9 and L1. When the electrode at T11 was also activated, there was no additional increase in respiratory function. As well as an acute increase in cough function DiMarco *et al.* [117] found that continued use of aSCS reduced the participant's reliance on a caregiver to provide an assisted cough (see Section 2.3.2.1) from 8.57 to zero times per week. In the follow-up study, DiMarco *et al.* [68] found the number of respiratory infections developed by each participant fell from a mean of 2.0 events per year pre aSCS, to 0.7 events per year after implantation. They also found that the use of aSCS led to fewer problems raising sputum, reduced need for suction, an improvement in the user's quality of life and an improvement in the control each user had on their breathing. All of these factors led to the users of aSCS having improved respiratory function.

The need for further surgery on the spinal cord to implant the aSCS electrodes, with an associated hospital stay, may deter people from having the procedure. DiMarco *et al.* [68] found that aSCS was associated with a large rise in blood pressure for three of the nine (33%) users studied. They also found that due to co-activation, whereby the electrodes used for aSCS activated any muscle controlled by nerves emerging from the stimulated nerve roots, aSCS led to a significant contraction of the muscles in the back and leg. They also report that a major drawback of aSCS is equipment failure rates of as high as 25 percent. These findings led Butler *et al.* [118] to conclude that while aSCS can be used to improve cough, it will only be implanted in a limited number of patients.

A summary of the pros and cons of the aforementioned techniques to improve the respiratory function of the tetraplegic population is presented in Table 2.2.

2.4.4 Abdominal Functional Electrical Stimulation

Abdominal Functional Electrical Stimulation (AFES) is the non-invasive application of a train of electrical pulses to the abdominal motor nerves, causing the abdominal muscles to contract (see Section 1.5.2). A number of studies have used AFES to improve the cough and

Table 2.2: A summary of the pros and cons of using Phrenic Nerve Pacing, Intramuscular Diaphragm Pacing, Magnetic Diaphragm Pacing, Intercostal Spinal Cord Stimulation, Intercostal and Abdominal Muscle Training, Magnetic Abdominal Stimulation and Abdominal Spinal Cord Stimulation to improve the respiratory function of the tetraplegic population.

Technique	Pros	Cons
Phrenic Nerve Pacing	Alternative to mechanical ventilation.	Invasive. Extensive surgical procedure. Expensive.
Intramuscular Diaphragm Pacing	Alternative to mechanical ventilation. Less invasive surgery than Phrenic Nerve Pacing.	Wires exiting skin pose risk of infection. Requires extensive training program.
Magnetic Diaphragm Pacing	Non-invasive.	Requires user to move neck.
Intercostal Spinal Cord Stimulation	Combined with Intramuscular Diaphragm Pacing to achieve ventilator free breathing. After training can achieve adequate inspired volumes.	Requires surgical procedure. Small initial inspired volumes. Hypertrophy of the upper trunk muscles.
Intercostal & Abdominal Muscle Training	Non-invasive. Easy to apply. Decrease in dyspnea.	Lack of control studies. Unclear whether intervention effect or natural recovery.
Magnetic Abdominal Stimulation	Less painful than electrical stimulation.	Requires mains power. Unportable. Risk of burns.
Abdominal Spinal Cord Stimulation	Reduced caregiver reliance for assisted cough. Reduced respiratory infection rate. Less problems raising sputum.	Surgical procedure. Significant contraction of the muscles in the back and leg. High rate of equipment failure.

quiet breathing of the tetraplegic population, in both an acute and long term manner, with these studies discussed in this section.

2.4.4.1 Acute Effect

The acute effect of AFES, or the immediate improvement in respiratory function that can be achieved by applying stimulation, has been observed during both quiet breathing and coughing.

Coughing In two almost simultaneous studies by Jaeger *et al.* [88] and Linder [89] AFES was used to produce a more effective cough for people with tetraplegia. In the study by Jaeger *et al.* AFES was applied to the rectus abdominis muscle, via electrodes situated on either

side of the umbilicus (see Figure 2.1(a)), of 24 tetraplegic participants (C4 to C7). They found that coughs produced with the assistance of AFES had a similar CPF as manually assisted coughs (3.83 ± 3.97 L/s) and a 13 percent greater CPF than voluntary coughs (3.83 ± 3.38 L/s). In the study by Linder, AFES was applied during the cough of eight tetraplegic participants, via electrodes situated on the abdominal wall. Linder showed an increase in MEP from 27.3 to 60 cmH₂O (120%) with the application of AFES, although this was lower than the MEP of 80 cmH₂O that could be achieved via a manually assisted cough.

Taylor *et al.* [119] applied AFES to the rectus abdominis muscles during coughing via two pairs of electrodes, with one electrode positioned below the costal margin and the other above the pubic symphysis on either side of the body (see Figure 2.1(g)). With a single participant they found an increase in CPF of 55 percent. This increase is greater than that found by Gollee *et al.* [72] who applied AFES to the rectus abdominis and external oblique muscles. The electrodes used to stimulate the rectus abdominis muscles were located in a similar position to that used by Taylor *et al.* and the electrodes used to stimulate the external oblique muscles were situated between the costal margin and the iliac crest (top of hip bone) (see Figure 2.1(f)). AFES was applied to four tetraplegic (C4 to C6) participants during cough and was found to lead to a mean increase in CPF of 40 percent, along with an increase in V_T of 31.5 percent. Butler *et al.* [118] also stimulated the rectus abdominis and external oblique muscle (see Figure 2.1(d)) to achieve an increase in CPF (36%), mean respiratory flow (80%) and FEV₁ (39%) during coughing. In this study one large pair of electrodes was used to stimulate both the rectus abdominis and the external oblique muscles, with the position used to stimulate the external oblique muscles more posterolateral (on the side and towards the posterior) than that used by Gollee *et al.*

Quiet Breathing In a preliminary study involving nine able bodied and one tetraplegic (C6/7) participant, Sorli *et al.* [120] applied AFES to the rectus abdominis muscles during quiet breathing via one pair of electrodes, situated above and below the umbilicus on the midline. They found that the V_T of the able bodied participants increased from 667 mL to 1100 mL (65%) during stimulation, with an increase also observed in the participant with tetraplegia. Stanic *et al.* [121] applied AFES to the rectus abdominis muscles of six able bodied and five tetraplegic (C4 to C7) participants during quiet breathing, via electrodes positioned in the same location as that used by Taylor *et al.* [119]. They found that the application of AFES increased the V_T of the able bodied participants by a mean of 34 percent (1370 versus 1026 mL), a similar absolute increase to that observed by Sorli *et al.* They also found that the tetraplegic participant's V_T increased by 35 percent (852 versus 629 mL) during stimulation, a similar increase to that observed by Gollee *et al.* [72].

Langbein *et al.* [71] applied AFES to the rectus abdominis muscles via four pairs of electrodes, positioned on either side of the umbilicus, with one pair located close to the costal margin and one pair located close to the pubic symphysis (see Figure 2.1(e)). They found that for

10 SCI (C5 to T7) participants, the application of AFES led to an increase in FVC (13%), FEV₁ (11%) and PEF (15%) compared to voluntary efforts. This increase in PEF is greater than that observed by Lee *et al.* [122] who found that the use of AFES with a posterolateral placement could increase the MEP (80%), PEF (10%), FVC (14%) and FEV₁ (23%) of one tetraplegic participant compared to their voluntary efforts. After a four week AFES training protocol the application of AFES was found to lead to a larger acute improvement in MEP (83%), PEF (32%), FVC (17%) and FEV₁ (25%) than before training.

Ventilated Patients Kandare *et al.* [123] used AFES to support ventilation in three tetraplegic (C0 to C2) participants who had complete diaphragm paralysis and were unable to breathe independently of either mechanical ventilation or a PNP device (see Section 2.4.1.1). AFES was applied to the rectus abdominis muscles via electrodes positioned in the same location as used by Taylor *et al.* [119] and to the external oblique muscles via a pair of electrodes placed parallel to those on the rectus abdominis muscle (see Figure 2.1(b)). The participants were able to achieve up to three minutes of unsupported ventilation. V_T was 25 percent less with AFES than with mechanical ventilation (0.83 versus 1.06 L), with the stimulated V_T being similar to that achieved by Stanic *et al.* [121]. This paper showed that AFES could be used to support ventilation with ventilated patients, in addition to ventilator-free patients, indicating an additional patient group who could benefit from AFES.

2.4.4.2 Long Term Effect

The long term effects of an AFES training program on cough and quiet breathing function has also been investigated in a number of studies.

Coughing McBain *et al.* [73] used AFES to train the abdominal muscles of 15 SCI participants (C4 to T5) by applying stimulation during five sets of 10 coughs per day, five days per week, for six weeks. AFES was applied to the rectus abdominis and external oblique muscles, using the same posterolateral electrode placement as Butler *et al.* [118]. They found that the application of AFES achieved an acute improvement in PEF of 50 percent. After the training period they found a statistically significant increase in stimulated PEF (16%) and unstimulated V_C (20%), FVC (12%), FEV₁ (8%) and PEF (14%).

Quiet Breathing Cheng *et al.* [124] applied AFES to the pectoralis major and rectus abdominis muscle, using the same electrode position as Taylor *et al.* [119], of 13 tetraplegic participants in the acute stage of injury, for 30 minutes per day, five days per week, for four weeks. Unlike Zupan *et al.* [114], who had earlier combined AFES with active RMT exercises, Cheng *et al.* used a passive intervention protocol, with participants not required to interact with the stimulation. The results were compared to 13 tetraplegic participants who had received no intervention. They found that after a four week training period V_C (32%), FVC (32%), FEV₁ (12%), PEF (33%), MIP (25%) and MEP (29%) had all increased, with a further increase observed both three and six months post intervention. All of the

respiratory measurements were statistically significantly greater for the intervention group than the control group after the training period. These results agree with the findings of McBain *et al.* who also found an increase in V_C , FVC, FEV_1 and PEF after an AFES training program.

McLachlan *et al.* [70] used a three week AFES training program, during which AFES was applied to the rectus abdominis and external oblique muscles of 12 tetraplegic participants (C3 to C6) using the same electrode position as Gollee *et al.* [72]. Stimulation was applied five days per week for a duration of 20 minutes per day in week one, 40 minutes per day in week two and 60 minutes per day in week three. Like Cheng *et al.* [124] this intervention protocol was also passive, with participants not required to interact with the stimulation. Like both Cheng *et al.* and McBain *et al.* [73], McLachlan *et al.* observed an increase in FVC (0.36 L), FEV_1 (0.18 L) and PEF (0.39 L/s)² after the AFES training program, and like Cheng *et al.* they also observed an increase in MEP (2.6 cmH₂O). Interestingly, some of the respiratory measures (notably FVC and MEP) had not plateaued after the three week training program, suggesting that a longer training intervention may be beneficial. They also found no increase in respiratory function during a one week pre-treatment and three week post-treatment control phase, suggesting that the intervention and not natural recovery was responsible for the increases in respiratory function. This suggests that while an AFES training program can be used to improve respiratory function, the optimum treatment duration has yet to be established.

Ventilated Patients Lee *et al.* [122] applied an AFES training program to one 65 year old tetraplegic (C4) who was eight months post injury and required non-invasive ventilation and a tracheostomy due to repeated respiratory infections caused by an ineffective cough and poor respiratory function. The AFES training program led to a 27 percent increase in unstimulated PEF and a 29 percent increase in FVC. This improvement in respiratory function allowed the patient to cough unaided after two weeks of AFES training and to have their tracheostomy removed after three weeks of training. They did not have a further respiratory infection in their 11 month hospital follow up. This suggests that AFES may be a suitable treatment modality to improve the respiratory function of ventilator dependant tetraplegics and may enable them to achieve faster weaning from mechanical ventilation.

Routsi *et al.* [125] applied FES to the leg muscles of acute ventilator dependant able patients in an intensive care unit and found that these patients weaned from mechanical ventilation at a statistically significantly faster rate than patients who did not receive FES. This suggests that FES may be preventing muscle atrophy and thereby improving the health status of the patient, enabling faster weaning from ventilation.

²Baseline, or percentage increases in, respiratory function were not published

2.4.4.3 Electrode Placement

Another challenge in the use of AFES is to establish the optimum electrode placement. A number of electrode placements have been used for AFES. These electrodes placements are shown in Figure 2.1 and discussed in further detail in this section.

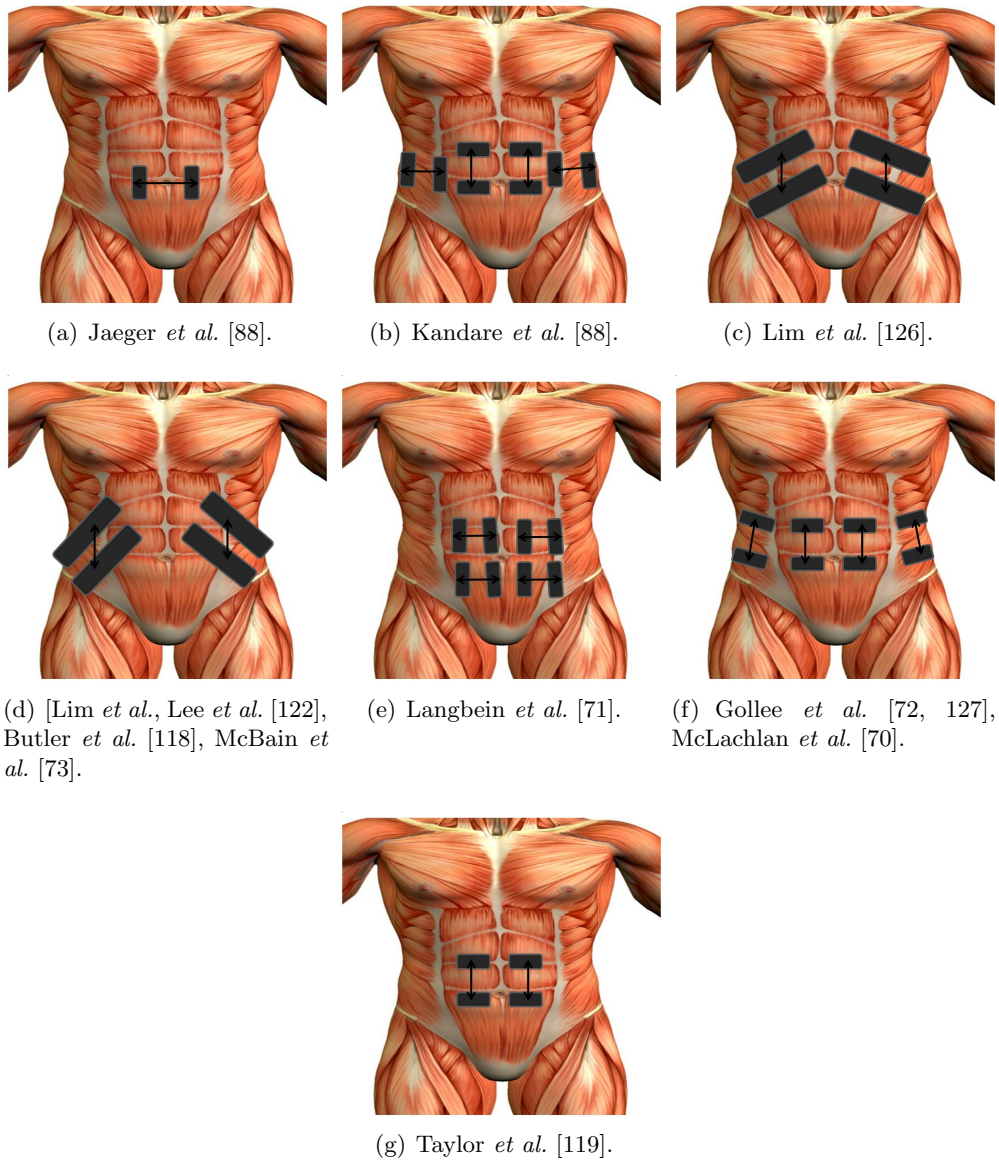


Figure 2.1: Diagram of the different electrode placements used to apply AFES. The authors who used each placement are shown in the caption for each subfigure.

In early studies AFES was only applied to the rectus abdominis muscles [88] (Figure 2.1(a)). Kandare *et al.* [123] included the stimulation of the external oblique muscles (Figure 2.1(b)), the most common electrode placement for studies involving AFES.

Lim *et al.* [126] used a gastroesophageal catheter to compare the gastric and esophageal pressures generated using two alternative AFES electrode positions. Large electrodes were used to stimulate both the rectus abdominis and external oblique muscles, with the external

oblique muscles being stimulated in both an anterior (Figure 2.1(c)) and posterolateral (Figure 2.1(d)) position. They found that at the highest intensity of stimulation, gastric pressure generated using the posterolateral placement was two and a half times greater than that generated using the anterior placement. No statistically significant difference in esophageal pressure was observed for the two electrode positions. They also observed that the application of magnetic stimulation (see Section 2.4.3.2) at T10 led to a statistically significant increase in both gastric and esophageal pressures, compared to AFES using the anterior placement. There was no significant difference in the pressures produced using magnetic stimulation or AFES using the posterolateral placement. They hypothesise that the superior results achieved using the posterolateral position is due to the posterolateral placement innervating the internal and external oblique, rectus abdominis, transverse abdominis and some of the intercostal muscles, with a greater degree of muscle recruitment than when using the anterior position.

Lee *et al.* [122] and Butler *et al.* [118] have both since used the posterolateral electrode placement suggested by Lim *et al.* (Figure 2.1(d)). The acute gains in quiet breathing function observed by Lee *et al.* were similar to those observed by Langbein *et al.* [71], who only applied stimulation to the rectus abdominis muscles (Figure 2.1(e)). After Lee *et al.* applied a four week AFES training program the acute improvements in respiratory function from AFES were greater than those observed by Langbein *et al.* The increase in CPF observed by Butler *et al.* was similar to that achieved by Gollee *et al.* [72] using an anterior electrode placement (Figure 2.1(f)), and less than that observed by Taylor *et al.* [119] who only stimulated the rectus abdominis muscles (Figure 2.1(g)). Therefore, the results achieved using a posterolateral electrode placement are inconclusive as to whether this position is superior to an anterior electrode placement.

The electrode placement that achieves the optimum muscle contraction when using AFES remains to be established. Sheffler and Chae [51] state that, when using FES, the strongest contraction of the target muscle is observed when stimulation is applied close to the muscle motor point (see Section 1.3). Studies by Gobbo *et al.* [52] and Botter *et al.* [128] used electrical stimulation to identify the position of the motor points of muscles in the leg, with Botter *et al.* reporting the position, intrasubject variability and uniformity of the motor points. A similar technique could be used to determine the position of the motor points of the abdominal muscles, which should be the optimum AFES electrode location.

2.4.4.4 Automated AFES System

The suitability of AFES for use in a clinical setting could be improved by the development of an automated AFES system. Such a system would allow AFES to be automatically synchronised with the user's respiratory activity, reducing operator dependence and allowing AFES to be applied consistently over extended periods of time. Synchronisation of such a system with a mechanical ventilator would also be useful for applying AFES with

acute ventilator dependent tetraplegic patients. Such a system would also allow different stimulation parameters to be applied for different breathing situations, such as quiet breathing and coughing, improving the effectiveness of cough generation. Development of such a system requires three main areas of focus, namely stimulation timing, classification of respiratory activity and identification of a suitable sensor to allow this timing and classification to be achieved.

Timing As the abdominal muscles are used for exhalation, AFES should only be applied during exhalation to avoid interfering with inhalation. Previous studies have used a manual input from the user [118, 119] or therapist [114] to apply stimulation at the correct point in the breathing cycle. The use of manual triggering has two drawbacks. Firstly, if AFES is being initiated by a therapist then they must be present at all times while AFES is being used. This has a cost implication for the health care provider. Secondly, the application of manual triggering is not as consistent as automatic triggering, especially over longer periods of time.

The signal from a spirometer, regarded as the ‘gold standard’ device for respiratory function measurement [129, 130], provides a direct measurement of respiratory flow and has been widely used to measure the respiratory activity of people with tetraplegia [34, 72, 127]. Gollee *et al.* [72], Sorli *et al.* [120] and Stanic *et al.* [121] have all developed AFES systems that are able to automatically trigger stimulation at the start of exhalation using the signal from a spirometer. All three studies reported an acute improvement in respiratory function when using AFES, along with a consistent application of stimulation. A spirometer is typically used with a full face mask, which is uncomfortable and intrusive, leaving the user unable to eat, drink or verbally communicate while in use. This limits the long term use of a spirometer within an AFES system, with a less invasive sensor being more suitable for this application.

Spivak *et al.* [90] developed a system that used an Electromyograph (EMG) signal from the respiratory muscles to automatically apply AFES during exhalation to assist coughing. They compared the PEF and FVC of 10 people with tetraplegia achieved using either EMG, caregiver or patient activated stimulation. They found that patient activated AFES actually resulted in a reduction in PEF and FVC, while caregiver and EMG activated stimulation produced a PEF and FVC similar to unassisted efforts. While the result of this study did not show any improvement in respiratory function with AFES, it did demonstrate the possibility of using the signal from a non-intrusive sensor to automatically apply stimulation at the correct point in the breathing cycle.

Classification To maximise the effectiveness of AFES, Gollee *et al.* [72] suggest that a quiet breath and a cough should be stimulated at different points in the breathing cycle, using different stimulation intensities. They suggest that during quiet breathing AFES should be applied at, or shortly after, the start of exhalation, to effectively support exhalation, while

during coughing stimulation should be applied at the end of inhalation to contribute to pressure build-up during glottal closure. A higher level of stimulation for coughing than for quiet breathing may also increase intrathoracic pressure, improving cough generation. To enable the application of the correct stimulation parameters at the correct point in the breathing cycle an automatic AFES algorithm must be capable of differentiating between a quiet breath and cough.

Gollee *et al.* [72] designed a system that used respiratory flow measurements, recorded using a spirometer, to identify a cough based on the inhalation flow rate and a quiet breath based on a cross-correlation algorithm. This system required manual setting of threshold values for the cross correlation and respiratory flow rate on a session by session basis. For clinical use, it would be desirable to minimise manual intervention during setup, resulting in a fully automated system.

Statistical classification, which is the principle of identifying the group an item belongs to using statistical methods, may be suitable for classifying respiratory activity. By using features within a signal statistical classification can be used to identify different groups. McCaughey and Gollee [131] used the signal from a spirometer as the input to a statistical classifier that made decisions based on a maximum likelihood algorithm. In this algorithm the features used for classification were selected manually for each participant. This manual selection of features is time consuming and not feasible in a clinical setting. A Support Vector Machine (SVM) is a statistical learning technique for binary classification problems. An SVM uses training data, marked as belonging to a certain group, to separate the data points in higher dimensional space by as large a margin (also referred to as a gap) as possible. The data points belonging to each group that are closest to this margin are called the support vectors. By assigning new data points to the same space, they can be classified as belonging to either group depending on their position relative to the support vectors.

When using an SVM data can either be separated linearly, using a linear kernel, or non-linearly, using a Radial Basis Function (RBF) kernel. However, even when using the correct kernel, data cannot always be separated cleanly. When this is the case the introduction of a soft margin technique can be used to control the generalization ability of the classifier. This soft margin technique splits data as cleanly as possible, allowing for misclassifications to occur to maximise the size of the margin. This technique is particularly useful when noise is present in a data set. In the case of a hard, or fixed margin, these noisy data points will determine the location of the support vectors. When using a soft margin these noisy data points are effectively ignored, allowing for a better and more stable separation of the data at very little cost to the classification ability. Adjustment of the soft margin must be done with care. If this boundary is too strict, or too loose, then some outliers will be assigned to the wrong class, with an associated negative impact on classification performance.

SVMs have a high generalization ability and good performance when compared to other classifiers [132]. They use automatic feature selection giving them an advantage over other classification techniques that require a greater degree of user input. Due to the low level of user input and high classification performance, SVMs are widely used in a clinical setting. Pradhapan *et al.* [133] used an SVM to successfully identify sleep apnea (pauses in breathing during sleep) from photoplethysmography data while Tenev *et al.* [134] used a combination of SVMs to use electroencephalography data to accurately identify attention deficit hyperactivity disorder in the adult population. The accuracy of an SVM was demonstrated by Qiu *et al.* [135] who used an SVM to predict the genotype of Hepatitis C Virus with an accuracy of 99 percent.

The use of an SVM is a possible solution for the automatic classification of respiratory activity within an AFES system. Such a system should allow a cough and a quiet breath to be stimulated at different points in the breathing cycle, with different stimulation parameters, increasing the effectiveness of an AFES system. The practicality of such a system could be further increased by replacing an intrusive spirometer, the ‘gold standard’ sensor for measuring respiratory function, with a non-intrusive sensor.

Non-Intrusive Sensors A number of non-intrusive sensors exist that could replace an intrusive spirometer for the detection and classification of respiratory activity within an automatic AFES system. Respiratory effort belts are made up of piezoelectric crystals which, when placed under stress such as a displacement, produce a change in voltage. This is known as the ‘piezoelectric effect’ (see Section 3.3.2 for further explanation of the piezoelectric effect). Respiratory effort belts are a well established method of detecting apnea during sleep studies, following offline respiratory activity analysis [136, 137]. The results of a single participant feasibility study by Gollee *et al.* [138] suggest that respiratory effort belts could be used to detect respiratory activity in real-time. They also show that the respiratory effort belt signal was not disturbed by the belt being placed on top of electrodes delivering AFES. This suggests that a respiratory effort belt may be a suitable sensor for real-time detection and classification of respiratory activity within an AFES system. A nasal thermocouple is a non-intrusive sensor that measures air temperature. As an inhaled breath is cooler than an exhaled breath, a nasal thermocouple is able to provide a qualitative measurement of breathing activity [139]. Farre *et al.* [140] suggest that nasal thermocouples are only semiquantitative devices, which do not have the ability to accurately quantify respiratory flow. This would suggest that while nasal thermocouples may have potential to be used to detect the correct point for stimulation, they may be unsuitable for classifying respiratory activity. Accelerometers have previously been used to record physical activity [141]. These sensors, positioned on the abdomen or chest, may be suitable for monitoring respiratory activity. Gollee and Chen [142] demonstrated that an Inertial Measurement Unit (IMU), which integrates accelerometers and gyroscopes to give an estimate of its relative orientation, could be used to detect respiratory activity. They also suggest that due to a difference in the

magnitude of the sensor signal during quiet breathing and coughing, that these sensors may be suitable for the classification of respiratory activity. While the small size of an IMU makes them suitable for a clinical setting, they are considerably more expensive than accelerometers. Additionally, the sensor used by Gollee and Chen was attached to an elastic belt, similar to a respiratory effort belt. Therefore, there is no obvious practical advantage to using an IMU when already using a cheaper respiratory effort belt. Therefore, this thesis will focus on the use of respiratory effort belts, nasal thermistors and accelerometers for breathing pattern detection and classification. The suitability of these sensors for real-time respiratory activity detection and classification remains to be investigated.

2.5 Conclusions

In conclusion, AFES has been shown to be a suitable method to improve cough and quiet breathing for the tetraplegic population. The non-invasive nature and easy application of AFES make it a potentially suitable system for use in a clinical setting. Despite these positive results AFES has yet to be adopted as a standard clinical treatment for the tetraplegic population. To aid this clinical introduction it would be beneficial to have an AFES system capable of automatically applying stimulation in synchrony with the user's respiratory activity, with stimulation effectiveness enhanced by applying it at the abdominal muscle motor points. Additionally, case studies have indicated that AFES may be suitable for improving respiratory function and assisting ventilator weaning for the ventilator dependent tetraplegic population. A larger study that investigates the feasibility and effectiveness of using AFES with the ventilator dependent tetraplegic population has yet to be conducted. Finally, the optimum training protocol for use of AFES with the sub-acute tetraplegic population and the combination of AFES with techniques currently used to improve respiratory function remain to be investigated.

Therefore, this thesis will aim to develop a system capable of the automatic application of AFES in a number of clinical settings. A simple technique capable of identifying the location of the abdominal muscle motor points will also be investigated. Finally, the feasibility and effectiveness of using AFES in a clinical setting with the ventilator dependent and sub-acute tetraplegic population, along with the integration of AFES with MI-E, will also be evaluated. This work should provide further evidence to support the clinical introduction of AFES for improving the respiratory function of the tetraplegic population.

Chapter 3

Experimental Methods

“Before anything else, preparation is the key to success.”

Alexander Graham Bell

3.1 Summary

This chapter introduces the methods used throughout this thesis to evaluate the feasibility and effectiveness of using Abdominal Functional Electrical Stimulation (AFES) to improve respiratory function. The methods used to measure the respiratory function of tetraplegic participants are explained here. The methods used to record respiratory activity, which allow AFES to be automatically synchronised with the user's own respiratory activity, are then outlined. The hardware, software and experimental set-up used to apply AFES with the able bodied and tetraplegic population, including a description of how respiratory activity was used to provide automatic stimulation, are then described. This chapter concludes by providing a description of the statistical methods used to evaluate the effectiveness of AFES.

3.2 Measurement of Respiratory Function

In this thesis respiratory function was evaluated by measuring Tidal Volume (V_T), Vital Capacity (V_C), Forced Vital Capacity (FVC), Forced Exhaled Volume in one second (FEV_1) and Peak Expiratory Flow (PEF). All of these measures, except for V_T , were calculated from the output of a FVC or V_C manoeuvre.

To conduct an FVC manoeuvre participants were instructed to inhale to maximum lung capacity and exhale as fully and as forcibly as possible, with verbal encouragement provided. To conduct a V_C manoeuvre the same procedure was followed, however participants were not asked, and not verbally encouraged, to exhale as forcibly as possible. The procedure for conducting an FVC or V_C manoeuvre is outlined in the American Thoracic Society (ATS)/European Respiratory Society (ERS) standards for spirometry [129], with these standards followed throughout this thesis. An FVC or V_C manoeuvre was deemed to be successful if:

- Breaths were free from artefacts such as a cough, early termination, leakage or an obstructed mouthpiece.
- Breaths had a satisfactory start i.e FEV_1 was acceptable (FEV_1 should be approximately 80 percent of FVC [43]).
- Breaths had a satisfactory exhalation *i.e.* participant was judged to have exhaled fully.

An example of features that would lead to an FVC or V_C manoeuvre being classed as unsuccessful are shown in Figure 3.1.

In the clinical study reported in Chapter 6 a V_C manoeuvre was performed up to five times, both with and without AFES, to form one run. A second run of V_C manoeuvres was then performed after V_T had been recorded. This resulted in each assessment session providing up to 10 stimulated and unstimulated V_C manoeuvres. Whether stimulation was applied during the first or second set of five V_C manoeuvres within each run was randomised for each participant at each session. In Chapter 7 an FVC manoeuvre was performed up to five times, both with and without AFES, to form one run. A second run of FVC manoeuvres

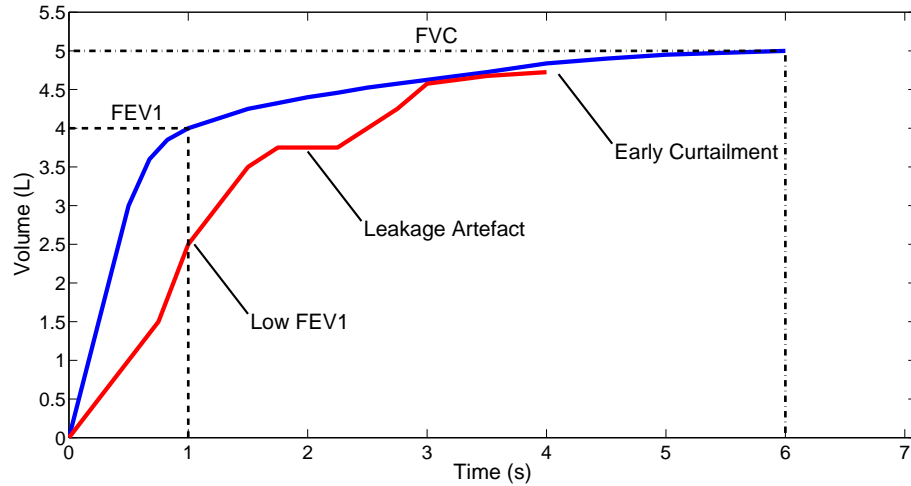


Figure 3.1: Example of a successful (blue) and unsuccessful (red) FVC manoeuvre. The manoeuvre shown in red was deemed unsuccessful due to i) an unsatisfactory start (identified from a low FEV_1) ii) a leakage artefact (identified from a plateau in the volume) and iii) the participant not exhaling fully (identified from early curtailment of the manoeuvre).

was then performed after a rest period of approximately two minutes. This resulted in each assessment session providing up to 10 stimulated and unstimulated FVC manoeuvres. As with Chapter 6, whether stimulation was applied during the first or second set of five FVC manoeuvres within each run was randomised for each participant at each session.

The validity of each FVC or V_C manoeuvre was checked offline and any attempts that did not meet the above criteria were rejected. FVC and V_C is the largest exhaled volume, of at least three successful FVC or V_C manoeuvres, which is within 0.15 L of another attempt. From the FVC or V_C manoeuvres FEV_1 and PEF were also calculated. FEV_1 is the largest volume recorded during the first second of an exhalation, of at least three successful FVC or V_C manoeuvres, which is within 0.15 L of another attempt. PEF is the largest exhaled flow rate, from at least three successful FVC or V_C manoeuvres, which is within 0.67 L/s of another attempt.

V_T was measured in Chapter 6 by asking participants to breathe normally for six minutes, or until their oxygen saturation level ($SaPO_2$) dropped below 92 percent. The participant's V_T was the mean of the values recorded during this six minute period. V_T was recorded both with and without AFES, with the order of these measurements randomised for each participant at each session. Stimulated and unstimulated measurement periods were separated by a break of two minutes, or until the participant's $SaPO_2$ returned to baseline, with participants being ventilated during this break if required.

To allow for effective group comparisons of respiratory function, the aforementioned measures of respiratory function were normalised by weight for each participant. This provided weight

corrected V_C (V_C/kg), V_T (V_T/kg), FVC (FVC/kg), PEF (PEF/kg) and FEV_1 (FEV_1/kg).

3.3 Respiratory Activity Sensors

Respiratory activity was recorded with a number of different sensors within this thesis, including spirometers, respiratory effort belts, nasal/oral thermocouples, accelerometers and pressure sensors. An example of the signals recorded using these sensors is presented in Figure 3.2, with these sensor signals explained in further detail in this section.

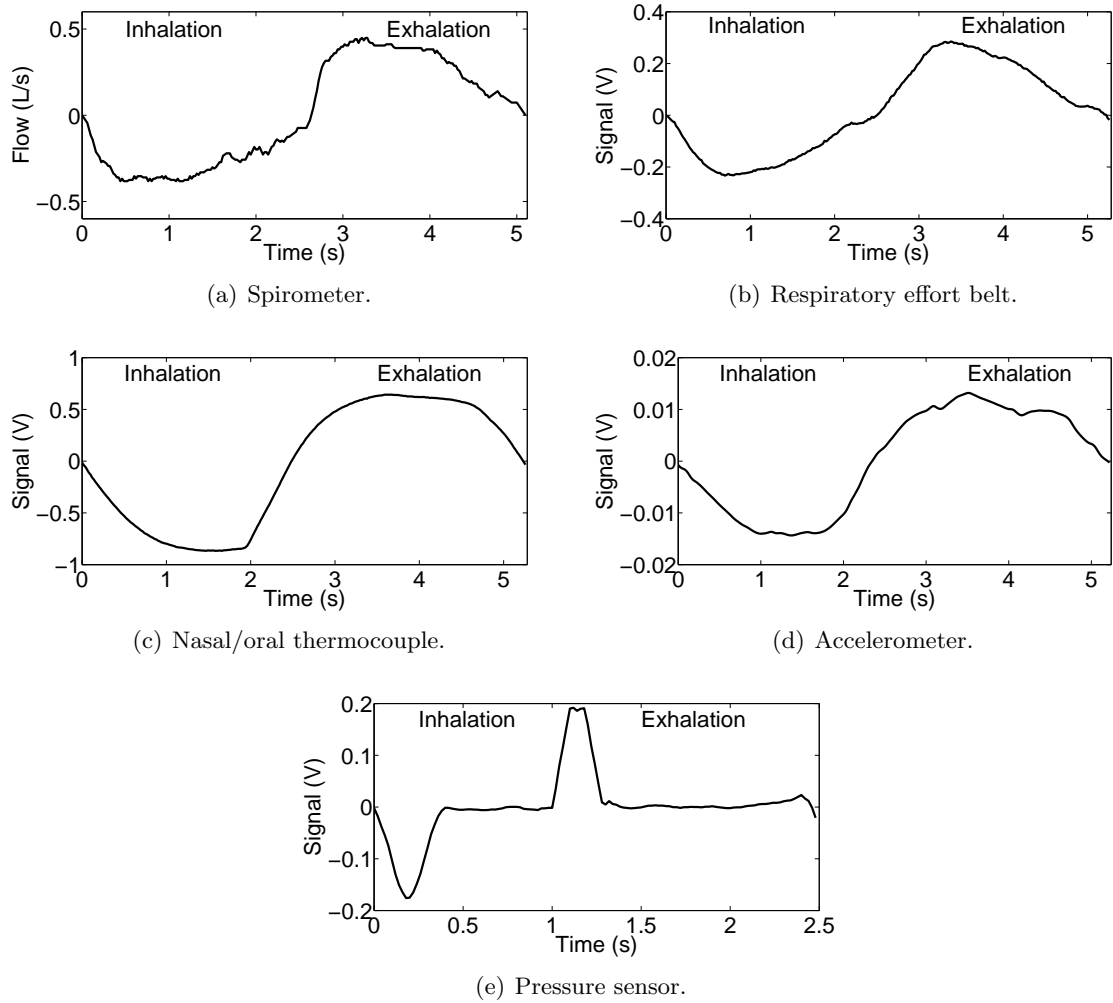


Figure 3.2: Example signals recorded using a spirometer, respiratory effort belt, nasal/oral thermocouple and accelerometer. These signals were all recorded during the same quiet breath from a human participant. Also shown is the signal recorded using a pressure sensor during a quiet breath provided by a mechanical ventilator. For all of these sensors a negative signal represents an inhalation and a positive signal represents an exhalation.

3.3.1 Spirometer

A spirometer (Microloop, Micromedical, UK), hereafter referred to as the Microloop spirometer, was used to record respiratory activity in Chapters 4, 6 and 7. This device uses

a turbine and light gate to measure respiratory activity. Every spin of the turbine, measured using the light gate, represents a volume increment. Multiplying the total number of volume increments within a specified sample time by the value of this volume increment provides the respiratory volume during that sample time. Respiratory flow rate is the derivative of this volume over the sample time. Whether this volume and flow rate was recorded during an inhalation or exhalation can be established from the direction of the turbine.

This spirometer provides both a flow signal, in litres per second (L/s), and a volume signal, in litres (L). The range and accuracy of this device is 0.1 to 8.0 L and 0.01 L when measuring volume and 0.2 to 15.0 L/s and 0.03 L/s when measuring flow rate. This spirometer signal was low pass filtered offline to smooth the signal (eighth order simple moving average filter, cut off frequency 2.7 Hz), necessary due to the use of volume increments to record respiratory volume, with a filtered spirometer flow signal recorded during a quiet breath shown in Figure 3.2(a). The spirometer was interfaced with a laptop computer using an RS232 interface.

To measure respiratory volume an interface is needed between the spirometer and the user. In Chapter 4 the spirometer was attached to a full face mask (Hans Rudolph Inc., USA) and in Chapters 6 and 7 the spirometer was attached to a mouthpiece, via a catheter mount tube. When the mouthpiece was used a nasal clip was also used to prevent air leakage at the nose, with participant's also instructed to form a seal at the mouth to prevent air leakage there.

In Chapter 7 respiratory activity was measured during Mechanical-Insufflation Exsufflation (MI-E) using a different spirometer, hereafter referred to as the ADInstruments spirometer. The ADInstruments spirometer was used here as, unlike the Microloop spirometer, it could be fitted in line with the MI-E device. In this system a spirometer pod (ML311, ADInstruments, New Zealand), which is a differential pressure transducer, was connected to a respiratory flow head (MLT1000L, ADInstruments, New Zealand), which contains a wire mesh at its centre. Air flowing through this wire mesh creates a pressure difference on either side, with a larger flow creating a greater pressure difference. This pressure difference, which is measured by the spirometer pod, is directly related to the flow rate.

This spirometer was designed to be used with the manufacturer's software (LabChart, ADInstruments, New Zealand) and amplifier, the gain of which was unknown. As the spirometer output was in Volts (V) it was necessary to calculate a calibration factor that allowed the flow rate, and in turn volume, to be calculated from this voltage signal. To find this calibration factor a 3 L syringe was used (3 Litre Calibration Syringe, Micromedical, UK). The full volume of the syringe was passed through the ADInstruments spirometer 100 times, at manually varying flow rates. The signal, which corresponds to flow and is measured in V, was integrated with respect to the sample time (0.02 s), with the maximum value of this integrated signal corresponding to the respiratory volume. The mean of the 100 maximum values was 0.0737 Volts seconds (Vs). By dividing the volume of the calibration syringe, which

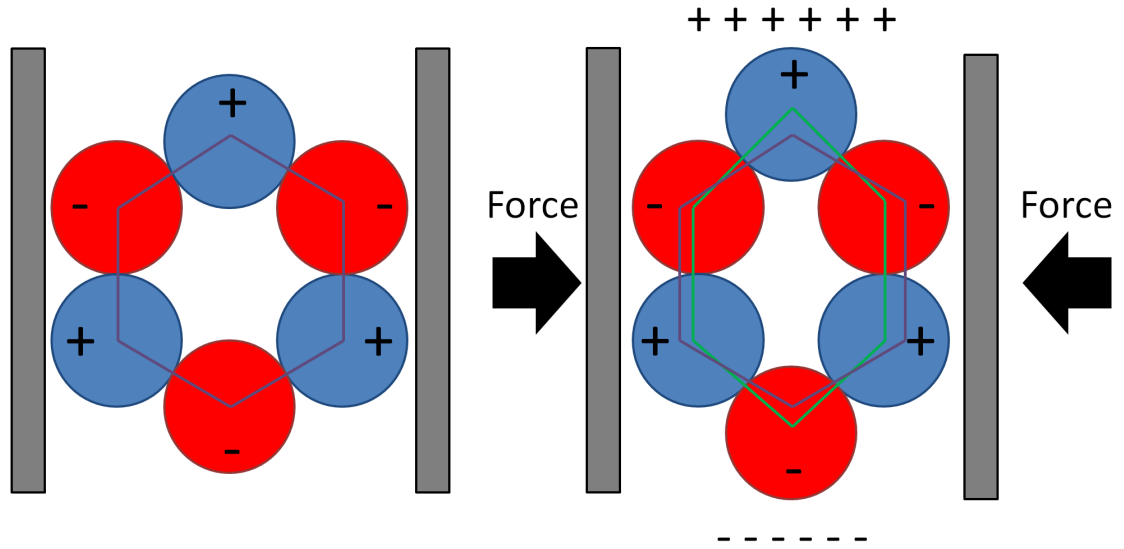
was known to be 3 L, by this mean value of 0.0737 Vs, it was found that a signal of 1 V corresponded to a flow rate of 40.7 L/s. This corresponds with the manufacturers suggested calibration factor of 40.1 L/s [143]. Therefore, the ADInstruments spirometer signal was multiplied by a calibration factor of 40.7 L/s to provide a respiratory flow in L/s, a signal which could be integrated to provide respiratory volume. The calibration syringe was also used to verify that the Microloop spirometer was properly calibrated.

The ADInstruments spirometer is capable of measuring flow rates in the range of ± 16.7 L/s, with a repeatability of 0.03 L/s. This spirometer had an in-built low pass filter (30 Hz) and was interfaced with a laptop computer using a 16-bit data acquisition card (NI DAQCard 6036E, National Instruments, TX, USA). It was fitted in line with the tubing connecting the participant and the MI-E device as shown in Figure 3.8.

3.3.2 Respiratory Effort Belts

Respiratory activity was also recorded using respiratory effort belts (Piezoelectric belts, ProTech, USA). These belts make use of the ‘piezoelectric effect’, whereby certain solid materials produce an electrical voltage when deformed. In an unstrained crystal, such as that shown in Figure 3.3(a), the positively and negatively charged atoms are separated symmetrically, causing the overall crystal structure to be charged balanced and no voltage to be produced. When a force is applied to the crystal, such as that shown in Figure 3.3(b), the symmetry of the charge separation is lost. This causes certain areas of the crystal to become positively and negatively electrically charged, causing a voltage to be generated. This voltage is proportional to the deformation of the material, hence respiratory effort belts positioned around the body can be used to measure the deformation of these areas during respiration. The signal from a respiratory effort belt is a measure of the stretch velocity of the belt and is directly related to the respiratory flow recorded using a spirometer. This sensor provides a signal in V, where a typical signal has a peak to peak amplitude of 600 μ V and the sensor has a sensitivity in the range of 2 to 30 μ V/mm. The respiratory effort belts were connected to a custom built amplifier that provided a gain of approximately 1000, a low pass filter (cut off frequency 15 Hz), high input-impedance and a high common mode rejection ratio. The respiratory effort belt signals were high pass filtered offline to remove signal bias (1st order butterworth, cut off frequency 0.04 Hz). In Chapter 4 these sensors were interfaced with a laptop computer via a 16-bit data acquisition card (NI DAQCard 6036E, National Instruments, TX, USA), while in all other chapters these sensors were interfaced via a 14-bit USB data acquisition card (NI USB-6009, National Instruments, USA). Figure 3.2(b) shows the amplified and filtered signal from a respiratory effort belt placed around the abdomen recorded during a quiet breath.

In Chapter 4 two respiratory effort belts were used to measure respiratory activity; one positioned around the participant’s abdomen, at the umbilicus, and the other positioned



(a) Charge balanced piezoelectric crystal.

(b) Charge unbalanced piezoelectric crystal.



(c) Respiratory effort belt.

Figure 3.3: Example of the piezoelectric effect. a) A charge balanced piezoelectric crystal, with the symmetry of the crystal shown in purple and the walls of the crystal shown in grey. b) The crystal is displaced by a compressive force, causing the upper surface of the crystal to adopt a more positive charge and the lower surface of the crystal to adopt a more negative charge. The new shape of the crystal is shown in green, with the previous, symmetrical, shape shown in purple for comparison. c) The respiratory effort belt used in this thesis, with the location of the piezoelectric crystal highlighted.

around the front of the chest, at the sternum. In Chapters 6 and 7 a respiratory effort belt was positioned around the abdomen to measure respiratory activity. The optimum set-up parameters for these respiratory effort belts were found in the study outlined below.

3.3.3 Respiratory Effort Belt Calibration

When using a respiratory effort belt to record respiratory activity a large signal magnitude is desirable, as this will result in a large signal to noise ratio. This should allow for more accurate measurement of respiratory activity. To establish the set-up parameters that provided the largest signal magnitude a servo motor was used to accurately displace a respiratory effort belt and the belt signal was recorded. The initial stretch, frequency of displacement and displacement of the belt that provided the largest signal magnitude was investigated in the experiment outlined below. When respiratory effort belts are used to measure respiratory activity the initial stretch of the belt is the only one of these three variables that is directly

under the operator's control. Therefore, the initial stretch that provided the largest signal magnitude was established first. This initial stretch was then applied to the belt when investigating the frequency and magnitude of displacement that provided the largest signal magnitude, both of which were deemed less within the operator's control as they are more dependant on the user's respiratory activity.

3.3.3.1 Methods

Equipment and Pre-processing A respiratory effort belt (Piezoelectric belt, ProTech, USA) was displaced by attaching it to a servo motor using a wire. The rotation of the servo motor, and hence displacement of the belt, was controlled using a closed loop feedback system implemented in the Simulink (Mathworks, USA) modeling environment. A diagram of the experimental set up is shown in Figure 3.4.

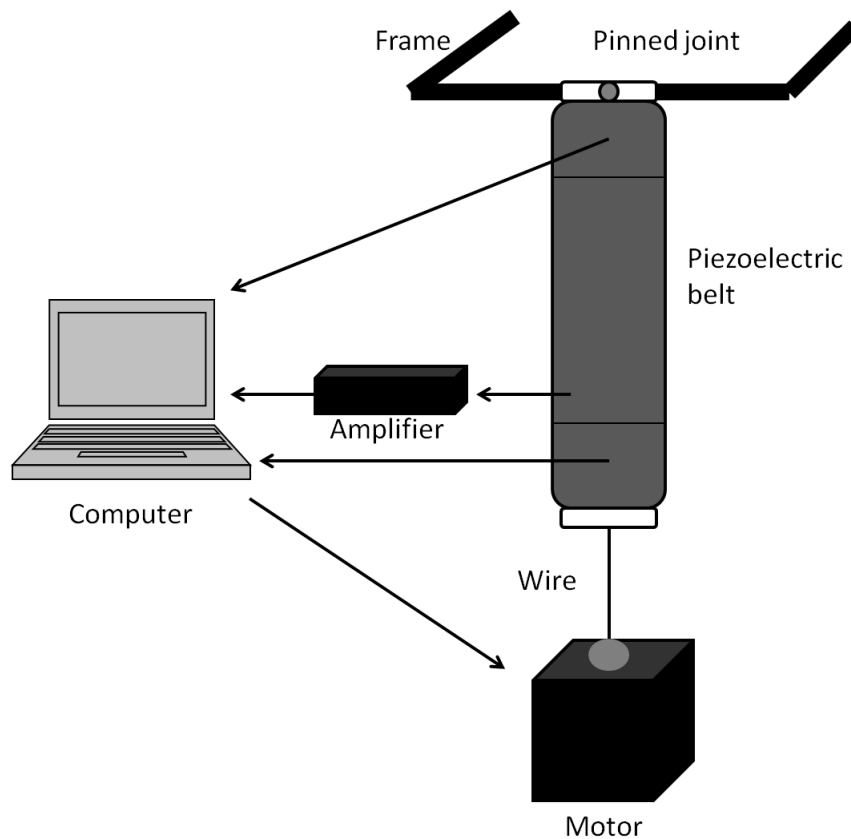


Figure 3.4: Experimental set up used to measure the magnitude of a piezoelectric belt signal under different conditions. Black arrows represent direction of data.

The belt signal was amplified using the custom amplifier described in Section 3.3.2. As the belt signal is directly related to the velocity of the belt, the signal was integrated to provide a signal relative to displacement, the variable being controlled by the feedback system. All data was recorded in Simulink using custom-made blocks to enable real-time data acquisition at a sample rate of 50 Hz.

The belt was tested under a number of different conditions, outlined below, to validate that

the signal from a respiratory effort belt is suitable for measuring respiratory activity and to establish the conditions under which the belt signal was largest.

Shape of Displacement The belt was displaced in a sinusoidal motion to provide a simple representation of the movement of the chest, or abdomen, during respiration. However, this movement is variable and can also be represented by a ramp. Therefore, the belt was also displaced using two different ramps. The first ramp had a rise and fall time equal to 50 percent of the total displacement duration. The second ramp had a rise and fall time of 40 percent of the total displacement duration, with the belt held at its maximum displacement for 20 percent of the total duration.

Initial Stretch An initial stretch of 0 cm was defined as the point where the belt was under enough tension to remove all slack but where the addition of any further tension would result in the belt being displaced from its initial position. To establish the initial stretch that provided the largest signal magnitude the belt was displaced with an initial stretch that was varied between 0 and 3 cm, in increments of 0.2 cm. This provided 16 measurement stretches. The initial stretch was set by hand using a measuring tape. During each initial stretch the belt was displaced by 2 cm for 60 s at a constant frequency of 0.2 Hz (chosen to correspond to the human respiratory rate, which is approximately 12 breaths per minute [144]). This movement provided 12 unique displacements, each of which had a unique maximum. The value of the signal at each of these maximum points was used for analysis.

Each test was repeated a further twice. The first maximum of each test was ignored due to potential noise, resulting in a total of 33 data points for each initial stretch value. The mean value of each of these data points was assumed to be the maximum signal amplitude for that displacement. After the initial stretch that provided the largest signal amplitude was established, this value of initial stretch was used for all further tests.

Frequency The effect of the frequency of displacement on the signal magnitude was analysed by displacing the belt at a frequency of between 0.1 and 0.5 Hz, in increments of 0.1 Hz, resulting in five measurement frequencies. The initial stretch was optimised from the information gathered from the previous test and the belt was displaced by 2 cm for 60 s. This resulted in six, 12, 18, 24 and 30 data points for each frequency respectively. Each test was repeated a further twice and the first maximum of each test was ignored. This resulted in a total of 15, 33, 51, 69 and 87 data points for each frequency of displacement. The mean value of the data points at each frequency was assumed to be the maximum signal amplitude for that frequency.

Magnitude of Displacement To establish the displacement that provided the largest signal magnitude the belt was displaced by between 0.2 and 5.0 cm, in increments of 0.2 cm, resulting in 25 measurement displacements. The belt was displaced for 60 s at a constant

frequency of 0.2 Hz and with a constant initial stretch, resulting in 12 measurement points. Each test was repeated a further twice and the first maximum of each test was ignored. This resulted in a total of 33 data points for each magnitude of displacement. The mean value of the data points at each displacement was assumed to be the maximum signal amplitude for that displacement.

3.3.3.2 Results

Shape of Displacement On all occasions the magnitude of the belt signal was greater when displacing the belt using a sinusoidal motion, compared to both forms of ramp.

Initial Stretch Figure 3.5 shows the maximum amplitude of the belt signal for each initial stretch, where each maximum is the mean of 33 maximums per displacement, taken from three recordings. For all three shapes of displacement the data takes the form of a concave, with an initial stretch of 0 cm having the largest signal magnitude, closely followed by an initial stretch of 3 cm. From an initial stretch of 2 cm the gradient starts to increase, with this trend continuing to the largest tested value of 3 cm.

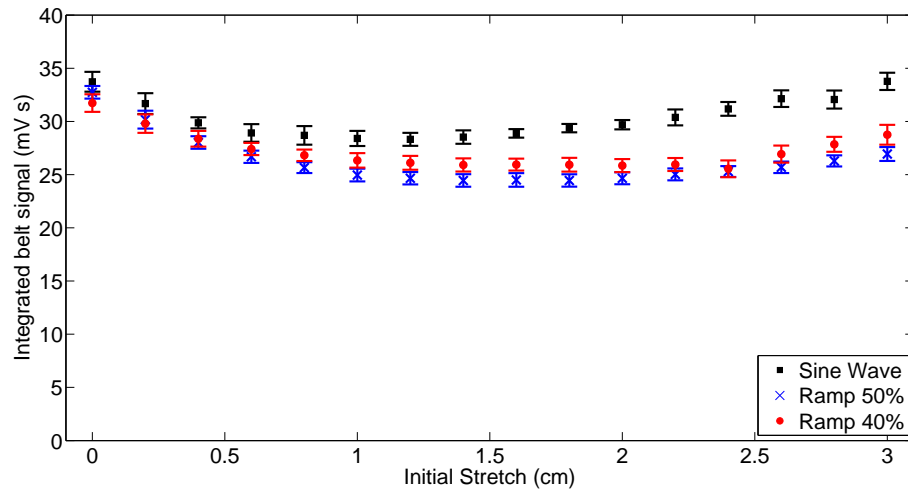


Figure 3.5: Maximum belt signal magnitude (mean \pm standard deviation) for varying initial stretch values. Belt was displaced by 2 cm at a frequency of 0.2 Hz using a sine wave (black), a ramp with a rise time corresponding to 50% of total displacement duration (blue) and a ramp with a rise and fall time corresponding to 40% of total displacement duration (red).

Frequency Figure 3.6 shows the maximum magnitude of the belt signal recorded when the belt was displaced at five different frequencies. Each maximum is the mean of 15, 33, 51, 69 and 87 maximums for each of the respective frequencies. The maximum magnitude of the signal was found to decrease with increasing frequency of displacement, with the maximum signal amplitude observed when the belt was displaced at a frequency of 0.1 Hz.

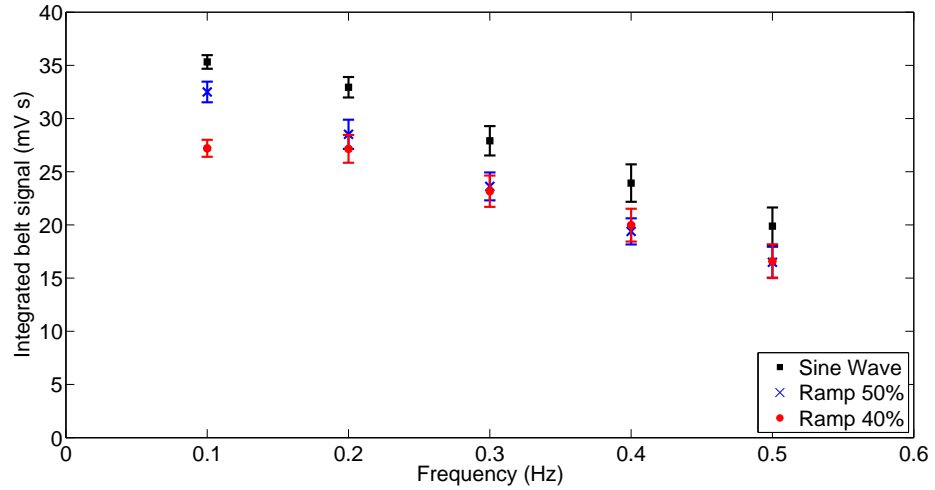


Figure 3.6: Maximum belt signal magnitude (mean \pm standard deviation) for varying frequency of displacement. Belt was displaced by 2 cm, with an initial stretch of 3 cm, using a sine wave (black), a ramp with a rise time corresponding to 50% of total displacement duration (blue) and a ramp with a rise and fall time corresponding to 40% of total displacement duration (red).

Displacement The maximum magnitude of the belt signal recorded when the belt was stretched to 25 different displacements is shown in Figure 3.7. Each maximum is the mean of 33 maximums recorded for each displacement. The maximum magnitude of the signal exhibits a linearly increasing response to increasing displacement. The largest maximum magnitude of the belt signal was observed at 5 cm for all three shapes of displacement.

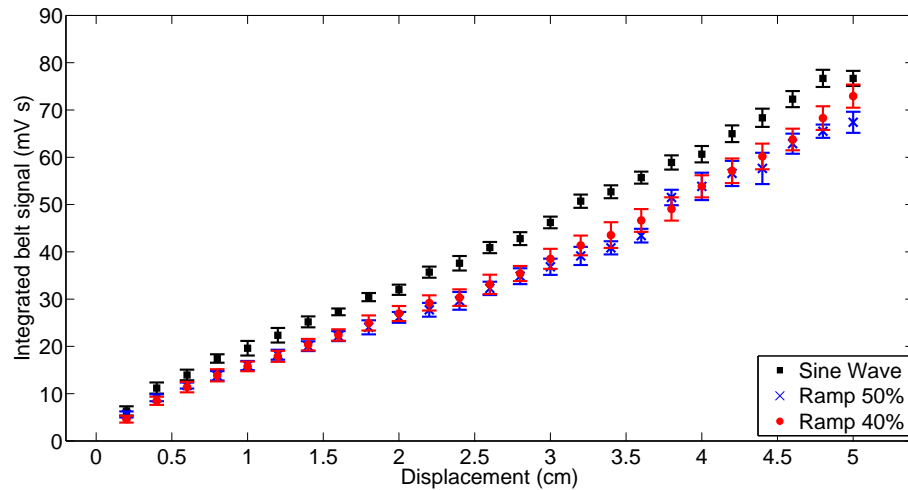


Figure 3.7: Maximum belt signal magnitude (mean \pm standard deviation) for varying displacement. Belt was displaced by 2 cm at a frequency of 0.2 Hz using a sine wave (black), a ramp with a rise time corresponding to 50% of total displacement duration (blue) and a ramp with a rise and fall time corresponding to 40% of total displacement duration (red).

3.3.3.3 Discussion and Conclusion

The largest magnitude of belt signal was observed when the belt was displaced from an initial stretch of 0 cm. However, an initial stretch of 0 cm is not practical for use with a human subject as any negative displacement from this point, such as would occur during an exhalation, would result in a ‘negative stretch’. During this time the belt signal would not change, rendering the belt unsuitable for measuring respiratory activity at these ‘negative stretch’ values. An initial stretch of 3 cm provided the largest signal magnitude away from the 0 cm point. The magnitude of the belt signal increased as the initial stretch was increased between 2 and 3 cm. This increase in magnitude may continue for initial stretches of greater than 3 cm. However, due to the tension that the initial stretch generates in the belt it was difficult to apply an initial stretch of greater than 3 cm using the servo motor. It was decided that 3 cm was the most suitable initial stretch value when using respiratory effort belts to measure respiratory activity.

The largest magnitude of the belt signal occurred when the belt was displaced at a frequency of 0.1 Hz, with only a small decrease in the magnitude of the signal when the belt was displaced at 0.2 Hz. The average human breathing rate is approximately 0.2 Hz, with the belt signal having a large signal amplitude when displaced at this frequency. This would provide a suitable signal to noise ratio at this frequency, hence respiratory effort belts were deemed suitable for measuring respiratory activity at these frequencies.

The magnitude of the belt signal increased linearly as the belt was displaced by an increasing amount. Therefore, larger displacements have a larger signal to noise ratio. As the magnitude of the movement of the chest, or abdomen, during respiration will vary between participants, the belt should always be placed in the position with the largest displacement. The magnitude of the signal was larger when the belt was displaced in a sinusoidal motion compared to a ramp. The shape of respiratory activity is outside of the operators control. However, having the user relax into a cyclic breathing pattern, which best represents a sinusoidal wave, will result in the largest signal magnitude.

One problem encountered when using piezoelectric crystals, such as those found within these piezoelectric respiratory effort belts, for measurements is ‘leakage’. Leakage causes the signal to slowly drifts back towards the baseline value during periods with no displacement, or displacement at a low frequency. During this experiment no evidence of leakage was observed, even when the belt was displaced at a frequency of 0.1 Hz.

It can be concluded that the set-up parameters outlined in this study should make respiratory effort belts suitable for measuring respiratory activity. Therefore, an initial stretch of 3 cm was applied to the respiratory effort belt for all use in this thesis. To allow for the greatest magnitude of displacement to be recorded the belt was positioned to detect the greatest

movement of the chest or abdomen. As the average human respiratory rate is approximately 12 breaths per minute [144], it was felt that respiration at this frequency would provide a signal magnitude that would provide a suitable signal to noise ratio.

3.3.4 Nasal/Oral Thermocouple and Tri-Axial Accelerometers

In Chapter 4 respiratory activity was also recorded using a nasal/oral thermocouple (ProTech, USA), placed on the participant's top lip. A nasal/oral thermocouple measures the temperature of air around prongs situated at the nose and mouth. As inhaled air has a lower temperature than exhaled air direction of respiratory flow can be calculated. This sensor provides a signal in V, where a typical signal has a peak to peak amplitude of 400 μV and the sensor has a sensitivity in the range of 2 to 30 $\mu\text{V}/\text{mm}$. The nasal/oral thermocouple was connected to an amplifier with similar characteristics to that used for the respiratory effort belts (see Section 3.3.2). In this thesis the amplified nasal/oral thermocouple signal was differentiated to allow comparison with the spirometer respiratory flow rate.

Two tri-axial accelerometers (ADXL 335, Analog Devices, USA), positioned on top of the respiratory effort belts located on the abdomen and chest, were also used in Chapter 4 to record respiratory activity. The accelerometers were used to measure acceleration with a range of $\pm 3.6 \text{ g}$ and a sensitivity of 300 mV/g. They provide an output in V, with a signal of 1 V equal to an acceleration of 0.7 g. They were connected to a custom built electronic subtractor, which was used to remove the gravitational offset from each of the accelerometer signals. Each accelerometer provides three separate acceleration signals in cartesian x, y and z coordinates. These signals were combined offline using a custom MATLAB (Mathworks, USA) script to provide one signal, in spherical coordinates, for each accelerometer. For all analysis within this thesis this acceleration signal was integrated, resulting in a velocity signal, which could be directly compared with the spirometer signal.

Both the nasal/oral thermocouple and accelerometer signals were high pass filtered offline to remove signal bias (first order butterworth, cut off frequency 0.04 Hz). In Chapter 4 these sensors were interfaced with a laptop computer using a 16-bit data acquisition card (NI DAQCard 6036E, National Instruments, TX, USA), while in all other chapters these sensors were interfaced using a 14-bit USB data acquisition card (NI USB-6009, National Instruments, USA). Figure 3.2(c) shows an amplified and filtered nasal/oral thermocouple signal recorded during a quiet breath, while Figure 3.2(d) shows the combined and filtered signal from an accelerometer placed on the abdomen recorded during the same quiet breath.

3.3.5 Pressure Sensor

In Chapter 6 a pressure sensor (HDIM050GBZ8H5, First Sensor AG, Germany) was connected to the filter located on the exhalation limb of a mechanical ventilator (Evita XL, Draeger, Germany) to provide a measure of the ventilatory flow. This pressure sensor

measures gauge pressure (pressure relative to the atmosphere) of gas (in this case air), with a range of ± 50 mbar and an accuracy of 0.75 mbar. It provides an output in V, with 1 V corresponding to 25 mbar. The pressure sensor signal was high pass filtered offline to remove signal bias (first order butterworth, cut off frequency 0.04 Hz) and interfaced with a laptop computer using a 14-bit USB data acquisition card (NI USB-6009, National Instruments, USA). A filtered pressure sensor signal recorded from a mechanical ventilator is shown in Figure 3.2(e).

This pressure sensor was also used in Chapter 7 to measure the flow from a MI-E device. To achieve this the pressure sensor was connected to a filter, fitted in line with the tubing between the participant and the MI-E device as standard clinical practice, to measure when insufflation and exsufflation were applied. This setup is shown in Figure 3.8.

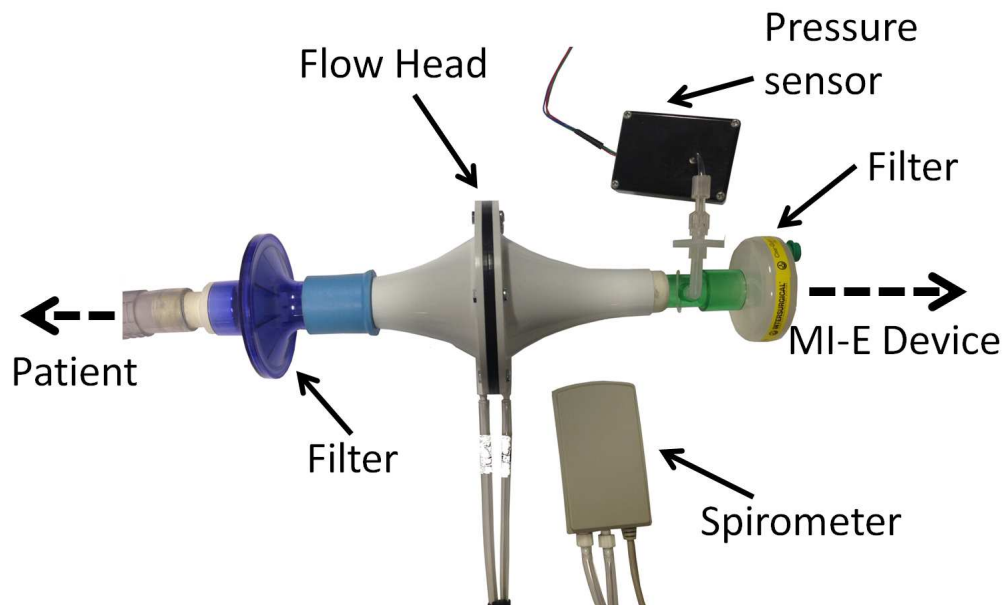


Figure 3.8: Spirometer interface used during Mechanical Insufflation-Exsufflation (MI-E). This shows the MI-E device, the respiratory flow head connected to the spirometer pod, filters to prevent secretions reaching the spirometer pod and a pressure sensor used to record respiratory activity. The filter on the right hand side of the image is the same filter as highlighted in Figure 7.2.

3.3.6 Software

All data was recorded in the Simulink modeling environment (Mathworks, USA) using custom-made blocks to enable real-time data acquisition at a sample rate of 50 Hz. A custom LabVIEW (National Instruments, USA) Graphical User Interface (GUI) was created and interfaced with the Simulink model using the LabVIEW simulation interface toolkit connection manager. This GUI displayed the sensor signals in real-time.

All of the MATLAB, Simulink and LabVIEW software used for data acquisition in this thesis,

and all of the MATLAB software used for data analysis, was created by the author.

3.4 Methods For AFES

AFES was applied and triggered in this thesis using a number of different methods, descriptions of which are provided below.

3.4.1 Stimulation System

A neuromuscular stimulator (RehaStim v1, Hasomed, Germany) was used to stimulate the abdominal muscles, bilaterally, using four stimulation channels. Bi-phasic current controlled stimulation pulses were applied at a frequency of 30 Hz and the pulsewidth varied between 100 and 500 μ s. Current was adjusted on a channel by channel basis until a visible muscle contraction was observed.

Stimulation was controlled using a custom built Simulink model. Once the criteria to trigger stimulation had been met (see Section 3.4.3) the model sent a signal to the stimulator, via a USB interface, initiating stimulation. The Simulink model was interfaced with a custom LabVIEW model, using the LabVIEW simulation interface toolkit connection manager. This LabVIEW model provided a GUI that allowed adjustment of the stimulation current, duration and trigger threshold in real-time and also displayed the stimulation pulsewidth. Stimulation pulsewidth was adjusted in real-time by the operator using a variable resistor shown in Figure 3.9.



Figure 3.9: Stimulation pulsewidth could be adjusted by the operator using a variable resistor. Two switches were also used to control stimulation, one which acted as a safety switch to stop stimulation being applied (shown in red) and one which allowed stimulation to manually be applied by the operator (shown in black).

This switch was interfaced with a laptop computer using a 16-bit data acquisition card in Chapter 4 and a 14-bit USB data acquisition card in all other chapters. Two switches, also shown in Figure 3.9, were interfaced in a similar manner. The first of these acted as a safety switch which, when pressed, prevented stimulation being applied while the program was running, even if the criteria to start stimulation was met. The second of these switches

allowed stimulation to be manually triggered by the operator. Both of these switch inputs were controlled within the Simulink model. The model also prevented stimulation from being triggered within one second of the previous stimulation burst ending.

3.4.2 Electrode Placement

During the studies outlined in Chapters 4, 6 and 7 stimulation was applied via four pairs of transcutaneous electrodes (33 mm x 53 mm rectangular, PALS, Axelgaard, USA) placed on the abdomen over the rectus abdominis and external oblique muscles on both sides of the body, as shown in Figure 1.10. In Chapter 4 the electrodes used to stimulate the external oblique muscles were placed horizontally, just below the bottom rib with a spacing of approximately 3 cm between the electrodes. The electrodes used to stimulate the rectus abdominis muscles were placed horizontally, approximately 2 cm horizontally and vertically from the umbilicus, with a spacing of approximately 3 cm between the electrodes. In the two clinical studies presented in Chapters 6 and 7 the electrodes were positioned horizontally around the motor point of the muscles, determined using the motor point location method described in Chapter 5, with a spacing of approximately 3 cm between the electrodes.

3.4.3 Automatic Stimulation

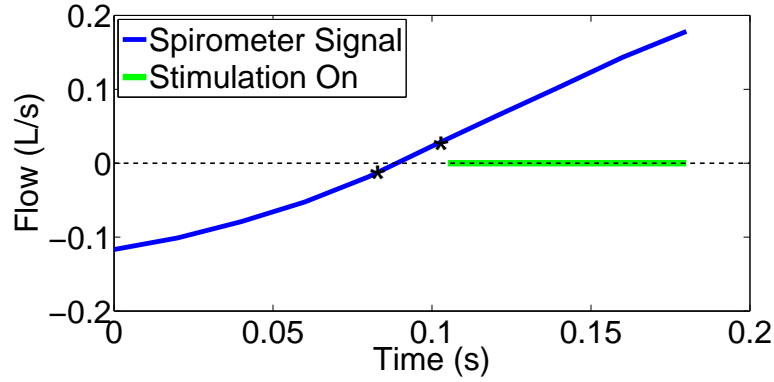
A number of the methods used to measure respiratory activity (see Section 3.3) were also used to automatically synchronise stimulation with the participant's respiratory activity. In all cases stimulation was applied at the start of exhalation for a period of 1 to 2 s (set manually using the LabVIEW GUI), with the exact duration dependant on the length of each participant's average exhalation.

In Chapters 4, 6 and 7 the signal from a spirometer was used to apply stimulation in synchrony with the participant's respiratory activity. Stimulation was applied at the start of exhalation, which was defined as a positive sample that proceeded a negative sample when the previous zero crossing was an inhalation (detected using the opposite logic). The signal from a respiratory effort belt was also used to apply stimulation in synchrony with the participant's respiratory activity. In this case the start of exhalation was defined as two consecutive positive samples, preceded by three non positive samples, where the previous zero crossing was an inhalation (detected using the opposite logic). If a participant was dependant on mechanical ventilation stimulation was automatically synchronised with the mechanical ventilator using the signal from a pressure sensor. The start of exhalation was defined as two samples with a value of greater than 0.05 V^1 (corresponding to a pressure of 1.25 mbar, used to avoid noise around 0 V) which preceded three samples with a value of less than 0.05 V, with the previous zero crossing being an inhalation (detected using the opposite logic). A graphical representation of these automatic triggering methods is shown in Figure 3.10. These three methods for triggering stimulation, along with the switch that could be used by the operator

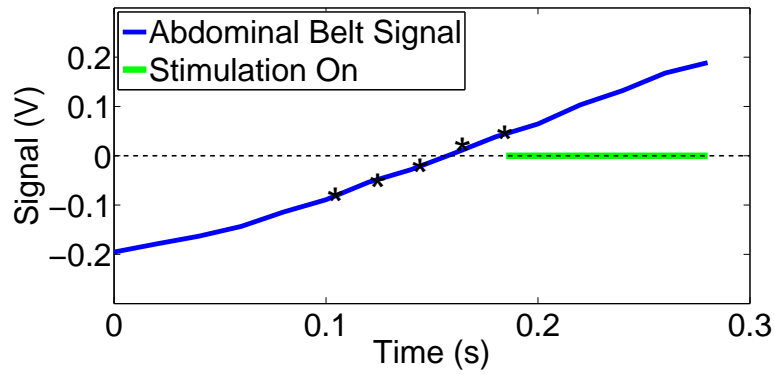
¹The stimulation threshold could be adjusted by the operator in real-time using the LabVIEW GUI

to apply stimulation (see Section 3.4.1), are shown in Figure 3.11.

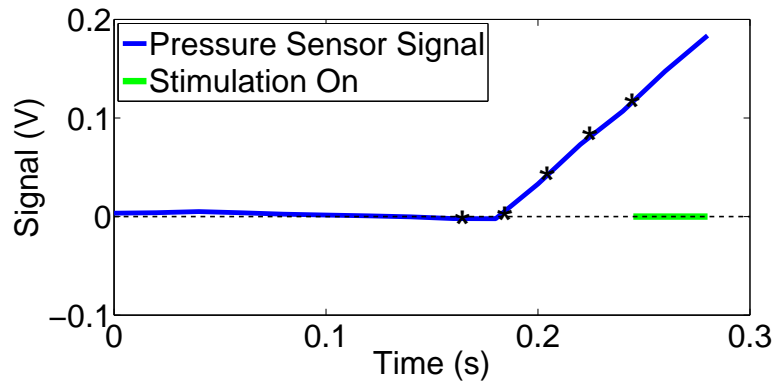
In Chapter 7 stimulation was automatically synchronised with MI-E using the signal from a pressure sensor. The criteria to start stimulation was the same as outlined for the pressure sensor above, with stimulation being applied for the whole exsufflation period of 3 s.



(a) Spirometer.

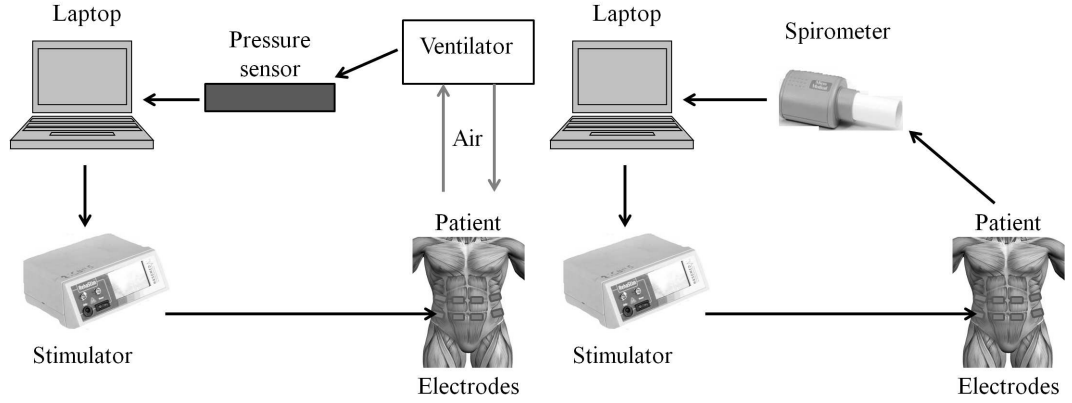


(b) Respiratory effort belt.

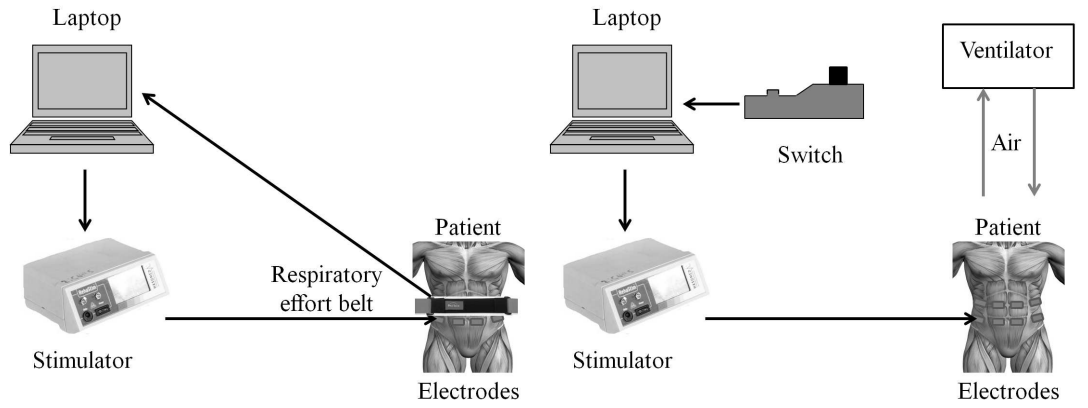


(c) Pressure sensor.

Figure 3.10: A graphical representation of the stimulation triggering algorithm for the spirometer, respiratory effort belts and pressure sensor. Figure 3.10(a) shows the stimulation triggering algorithm for the spirometer. When using the signal from the spirometer stimulation is automatically applied after detection of a negative sample (individual samples are shown by black *) directly followed by a positive sample when the previous zero crossing was an inhalation (detected using the opposite logic). Figure 3.10(b) shows the stimulation triggering algorithm for the respiratory effort belts. When using the signal from the respiratory effort belts, in this example the respiratory effort belt positioned around the abdomen, stimulation is automatically applied after the detection of three negative samples preceded by two positive samples, when the previous zero crossing was an inhalation (detected using the opposite logic). Figure 3.10(c) shows the stimulation triggering algorithm for the pressure sensor. When using the signal from the pressure sensor stimulation is automatically applied after the detection of three samples less than 0.05 V preceded by two samples greater than 0.05 V, when the previous zero crossing was an inhalation (detected using the opposite logic). In all figures the point where stimulation is applied is shown by a green line.



(a) Pressure sensor used when participant was connected to mechanical ventilation. (b) Spirometer used during assessment sessions.



(c) Respiratory effort belt used during training sessions. (d) Manual switch which could be used to apply stimulation at all times.

Figure 3.11: Experimental set up showing the four sensors used to trigger stimulation in synchrony with the user's respiratory activity. Black arrows indicate direction of data.

3.5 Statistical Analysis

A number of statistical tests were used in this thesis. They were employed to test for normality of data, linear dependance, statistical significance and to measure the effect size of an intervention. All of these statistical calculations were performed using the MATLAB statistics toolbox (version 7.3).

3.5.1 Normality

The normality of a data set affects the test employed to test for statistical significance. In this thesis normality was tested using the Shapiro-Wilk test of normality, which tests the null hypothesis that a sample originates from a normally distributed population. If the p-value is found to be smaller than the chosen significance, or alpha level (in this thesis set at 0.05 for all statistical tests), then the null hypothesis is rejected and it can be assumed that the data does not come for a normally distributed population. This test was chosen as it has been shown to be the most powerful normality test [145].

3.5.2 Linear Dependence

A Pearson product-moment Correlation Coefficient (PCC) was used to test for linear correlation, or dependence, between two data sets. The PCC, calculated as the covariance of two data sets divided by their standard deviation, is a value between one and minus one. A value of one indicates a total positive correlation (*i.e* all data points lying on a linear line and as one data set increases so does the other), minus one indicates a total negative correlation (*i.e* all data points lying on a linear line and as one data set increases the other decreases) and a value of zero shows that there is no correlation between the data sets. If the data could not be represented by a linear line a PCC of greater than 0.8 was regarded as a strong positive correlation.

3.5.3 Significance Testing

Three different statistical tests were used in this thesis to test for statistical significance, with the choice of test depending on whether the data was normally distributed or not. For all significance testing the significance level, or p-value, was set as 0.05, with a p-value of less than 0.05 deemed statistically significant.

3.5.3.1 Parametric Test

For data that was found to be normally distributed, or parametric, when using a Shapiro-Wilk test, an analysis of variance (ANOVA) was used to test for a statistically significant difference between data sets. This test, which allows a significance test to be performed on more than one group of data, provides an indication of whether the means of the groups are equal. This is found by calculating the within and between group variances, both of which should be equal if the means of the two data sets are equal, or different if the means differ. In the case where a statistically significant difference between means was found, post hoc multiple comparison testing was performed using the Tukey-Kramer honest significant difference test. This test compares the mean of every group with the mean of every other group to identify differences between pairs of means that are greater than the expected standard error, calculated using the ANOVA test. When analysing individual participant's data a one-way ANOVA was performed and when analysing grouped data, where the data was collected from the same group of participants at different time points, a two-way repeated measures ANOVA was performed.

An independent Student's t-test is used to test the null hypothesis that the difference between two independent data sets comes from a normal distribution that has a mean of zero. An independent Student's t-test was used in this thesis to test for a statistically significant difference between the means of two different groups, where the data within each group was found to be normally distributed. A one-way ANOVA is an extension of the Student's t-test for comparing the means of at least three groups.

3.5.3.2 Non-parametric Test

For data that was found to not be normally distributed, or non-parametric, when using a Shapiro-Wilk test, a Kruskal-Wallis test was used to test for a statistically significant difference between groups of data sets. This test, which is the non-parametric equivalent of a one-way ANOVA, allows a significance test to be performed on more than one group of data and provides an indication of whether the groups originate from the same distribution. This is found by summing the ranks of both groups and calculating the test statistic. In the case where a statistically significant difference was found, post hoc multiple comparison testing was performed using the Tukey-Kramer honest significant difference test, with the expected standard error calculated using the Kruskal-Wallis test.

When comparing two groups of data that were found to not be normally distributed when using a Shapiro-Wilk test, and found to be linearly correlated, using a PCC test, a Wilcoxon signed-rank test was used to test for statistical significance. This test provides an indication of whether the medians of two groups are statistically significantly different by firstly comparing the pre and post treatment values, then ranking them and applying a sign to the rank (*i.e.* negative if the post treatment value was less than the pre treatment value and vice-versa). The positive and negative ranks are then summed and the lowest value of the negative and positive summed values provides the test statistic. If this test statistic is greater than the critical value for the test criteria, computed from standard statistical tables, then the null hypothesis (that the data comes from a distribution with the same median) cannot be rejected.

3.5.4 Effect Size

While significance testing provides an indication of whether the mean, or median, of two different groups is statistically significantly different, it does not provide an indication of the size of this difference. In intervention studies with a large enough sample size, any differences, or effect, will be found to be statistically significantly different, even when this difference has no practical importance or is not clinically relevant. Likewise, a study with a small sample size can show a large effect, which is clinically relevant, even when no statistically significant difference is shown. Effect size is a way of quantifying the size of an intervention effect. In this thesis the effect size of an intervention is quantified using Cohen's *d* [146], which expresses the difference between two means in standard deviation units *i.e.* a Cohen's *d* of one implies that the means are different by one standard deviation. An effect size less than 0.2 is regarded as small, 0.5 medium and greater than 0.8 large [146]. It should be noted that a large effect size between two means can be detected even when the difference between these two means is not statistically significant. Cohen's *d*, d , is calculated using Equation 3.1, where \bar{x} is the mean of the value being analysed before (1) and after (2) an intervention has been applied.

$$d = \frac{\bar{x}_1 - \bar{x}_2}{s} \quad (3.1)$$

The pooled variance, s , is calculated using Equation 3.2, where n is the number of sample

points and s is the standard deviation of the data before (1) and after (2) an intervention has been applied.

$$s = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}} \quad (3.2)$$

The margin for error within an effect size estimate can be analysed using confidence intervals. If these confidence intervals show that the lower confidence is greater than zero then it can be concluded that there is almost certainly a positive effect from the intervention. The confidence interval, c , of the effect size was calculated in this thesis using Equation 3.3.

$$c = \sqrt{\frac{n_1 + n_2}{n_1 n_2} + \frac{d^2}{2(n_1 n_2)}} \quad (3.3)$$

It should be noted that when using an ANOVA to test the effect of an intervention Eta-squared η^2 can be used to estimate the amount of the variance between the pre and post intervention results that can be explained by the intervention (*i.e* the effect size). η^2 is a ratio between the sum of the squares of the treatment ($SS_{Treatment}$) and the total sum of the squares (SS_{Total}) and can be calculated using Equation 3.4.

$$\eta^2 = \frac{SS_{Treatment}}{SS_{Total}} \quad (3.4)$$

This calculation tends to seriously over estimate the size of the effect, especially when using a small sample size, as it is a sample based estimate [147]. Therefore, due to the low sample sizes in the studies reported in this thesis, Cohen's d was used to quantify the effect size, even when using an ANOVA.

Chapter 4

Real-time Detection and Classification of Respiratory Activity For Automatic Abdominal Functional Electrical Stimulation

*“In every branch of knowledge the progress is proportional to the amount of facts on which
to build, and therefore to the facility of obtaining data.”*

James Maxwell

4.1 Summary

The effectiveness of Abdominal Functional Electrical Stimulation (AFES) can be enhanced by using different stimulation parameters, optimised for quiet breathing and coughing. Previously, respiratory flow, measured using a spirometer coupled with an intrusive facemask, has been used to detect and differentiate between these two breath types allowing the correct stimulation parameters to be applied. In this chapter five non-intrusive sensors were evaluated for their suitability to detect respiratory activity in real-time. The signals from two of these sensors, respiratory effort belts positioned around the chest and the abdomen, were then used for real-time breathing pattern classification. In this work, which has been published in *Medical Engineering and Physics* [148], a Support Vector Machine (SVM) algorithm was trained on a participant by participant basis to classify respiratory activity as either quiet breathing or coughing. By using the signal from the respiratory effort belt positioned around the chest the SVM could be used to achieve an acceptable classification performance compared to that achieved using the signal from a spirometer. The signal from the belt positioned around the abdomen and a combination of both belt signals resulted in a lower classification performance. This novel SVM algorithm could be incorporated into an automatic AFES device, designed to improve the respiratory function of people with tetraplegia.

4.2 Background

AFES has been shown to improve the respiratory function of people with tetraplegia (see Section 2.4.4). Gollee *et al.* [72] show that the effectiveness of AFES could be improved by using different stimulation parameters for quiet breathing and coughing. They suggest that quiet breaths should be stimulated at the start of exhalation, to support exhalation and avoid interfering with an inhalation, while coughs should be stimulated during glottal closure (between the end of inhalation and the start of a cough exhalation) with a higher level of stimulation than a quiet breath. This would increase intrathoracic pressure and aid cough generation.

A number of AFES systems have been developed which i) detect respiratory activity to allow AFES to be applied at the correct point in the breathing cycle and ii) differentiate between quiet breathing and coughing, enabling different stimulation parameters to be applied for each breath type (see Section 2.4.4.4). Many of these systems use the signal from a spirometer. A spirometer is typically coupled with a full face mask which is uncomfortable and intrusive, leaving the user unable to eat, drink or verbally communicate while in use. Using a non-intrusive sensor, such as those described in Section 2.4.4.4, would make these systems considerably more practical. Additionally, the systems previously used to classify respiratory activity require operator intervention to optimise classification performance. This is time consuming and unsuitable in a clinical setting. The use of a statistical classifier based on an SVM (see Section 2.4.4.4) could decrease the need for operator intervention, making

such an AFES system more suitable for a clinical setting.

The two aims of this study were i) to identify a non-intrusive sensor capable of detecting respiratory activity in real-time, and ii) to develop a classification algorithm capable of using the signal from this non-intrusive sensor to classify respiratory activity in real-time, with minimal operator intervention.

4.3 Methods

Ten able bodied participants (six males, four females, age 27.6 ± 5.2 years (mean \pm standard deviation) [range 24 : 40 years]) were recruited for this study and asked to attend two sessions, described below. The study was approved by the Faculty of Biomedical and Life Sciences ethics committee at the University of Glasgow (Local Code: FBLS 1034). All procedures conformed to the declaration of Helsinki and all participants gave written informed consent.

4.3.1 Equipment

The participant's respiratory activity was recorded using a spirometer, two respiratory effort belts, a nasal/oral thermocouple and two tri-axial accelerometers, as described in Section 3.2. A diagram of this experimental set up is shown in Figure 4.1.

All data was recorded on a laptop computer in the Simulink modeling environment (Mathworks, USA) at a sample rate of 50 Hz. The spirometer was connected to the laptop computer using an RS232 interface and the respiratory effort belts, nasal/oral thermistor and accelerometers were connected using a 16-bit data acquisition card (NI DAQCard 6036E, National Instruments, TX, USA). The respiratory effort belt, nasal/oral thermocouple and accelerometer signals were high pass filtered offline to remove signal bias while the spirometer signal was low pass filtered to smooth the signal. This pre-processing is described in further detail in Section 3.3.

4.3.1.1 Stimulation System

Stimulation was applied using the system described in Section 3.4.1. Stimulation current was adjusted on a channel by channel basis for each participant (with a pulsewidth of $100 \mu s$) until a visible contraction was observed (range 10 to 60 mA for all participants), with this current remaining fixed for the remainder of both sessions. Stimulation pulsewidth was varied between 100 and $150 \mu s$ within each session to account for muscle fatigue. Stimulation was automatically applied for 1.5 seconds for a quiet breath and one second for a cough at the start of exhalation, in synchrony with the participant's respiratory activity, using the signal from the spirometer. This automatic application of stimulation is described in further detail in Section 3.4.3.

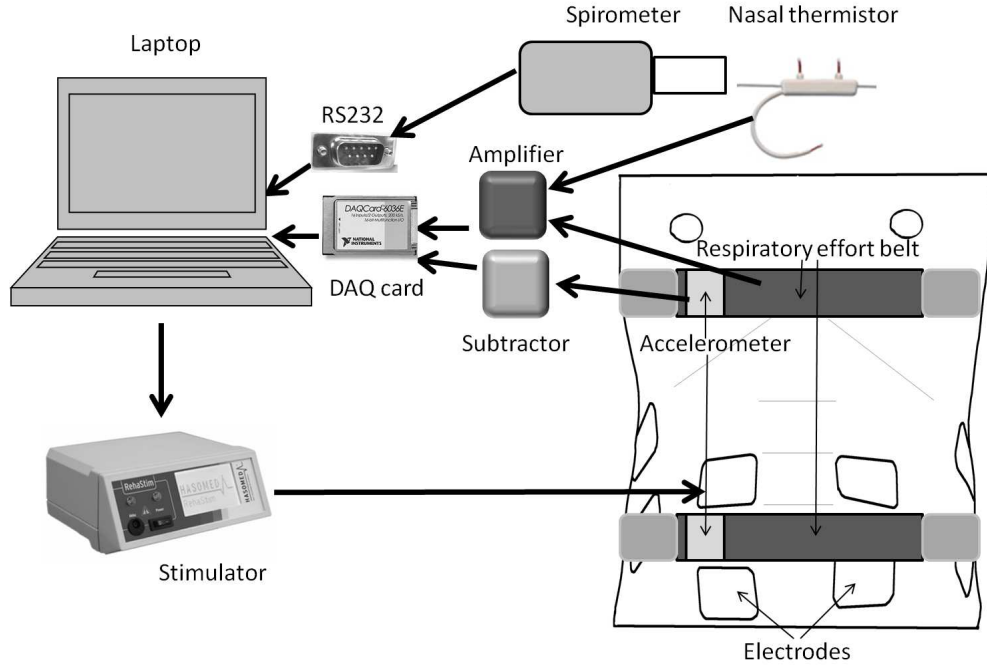


Figure 4.1: Experimental set up showing methods used to record respiratory activity; namely a spirometer, two respiratory effort belts, a nasal/oral thermocouple and two tri-axial accelerometers. Also shown is a stimulator and electrodes used to apply AFES, a laptop computer used to record data, a RS323 interface used to connect the spirometer to the laptop, an amplifier used to amplify the signals of the respiratory effort belts and the thermocouple, an electronic subtractor used to remove the gravitational offset from the accelerometer signals and a DAQ card used to connect the respiratory effort belts, accelerometers and the thermocouple to the laptop. Bold arrows represent direction of data. Thin arrows indicate items.

4.3.2 Data Collection Protocol

The data collection protocol is summarised in Figure 4.2. Experimental sessions included runs consisting of approximately six to ten coughs and one minute of quiet breathing, with and without the support of AFES. The order of each of these four breath types within each run was randomised, with each breath type following directly one after the other. Each run was repeated three times per session, separated by a rest period of approximately two minutes. The session was repeated after a period of approximately seven days.

The data recorded during the two sessions was combined for each participant. Data sets containing all of the cough data or all of the quiet breathing data were then created for each sensor, for each participant.

4.3.3 Analysis

The suitability of the non-intrusive sensor signals for real-time detection of respiratory activity was evaluated by analysing the time shift of these signals relative to the respiratory flow measured by the spirometer. In a second step, the signals found to be suitable for real-time respiratory activity detection were used to construct SVMs, and the ability of these SVMs

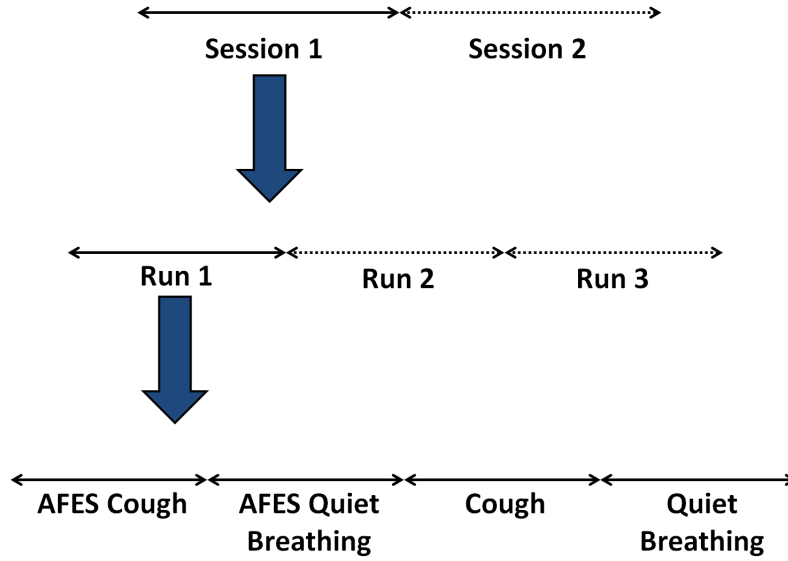


Figure 4.2: Protocol showing two sessions, split into three runs, with each run containing a period of AFES assisted and unassisted quiet breathing and coughing.

to accurately classify respiratory activity as quiet breathing or coughing was evaluated.

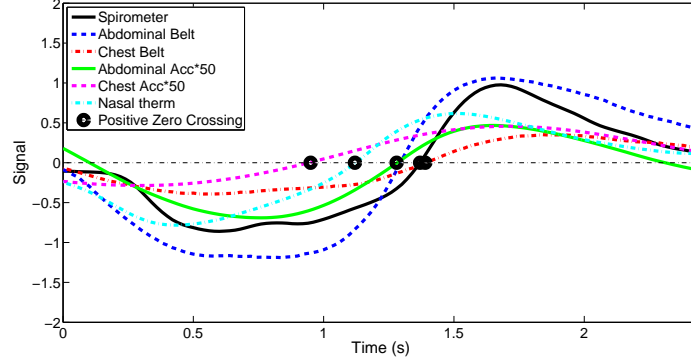
4.3.3.1 Time Shift

To determine the suitability of the non-intrusive sensors for real-time detection of respiratory activity, the time shift between the start of exhalation detected by each of the non-intrusive sensor signals and the spirometer signal was calculated for all breaths recorded from each participant (approximately 100 coughs and 200 quiet breaths). The spirometer signal provides a direct measurement of respiratory flow, with positive values corresponding to exhalation and negative values representing inhalation. A positive zero crossing of the spirometer signal (*i.e.* from a negative to a positive value as marked on Figure 4.3) was taken to represent the start of exhalation. For the non-intrusive sensors, the start of exhalation was defined as two consecutive positive samples, preceded by three non positive samples, where the previous zero crossing was an inhalation (detected using the opposite logic). Due to the high signal to noise ratio achieved using the filtering techniques described in Section 3.3 these methods were found to be robust enough to minimise false positive detection.

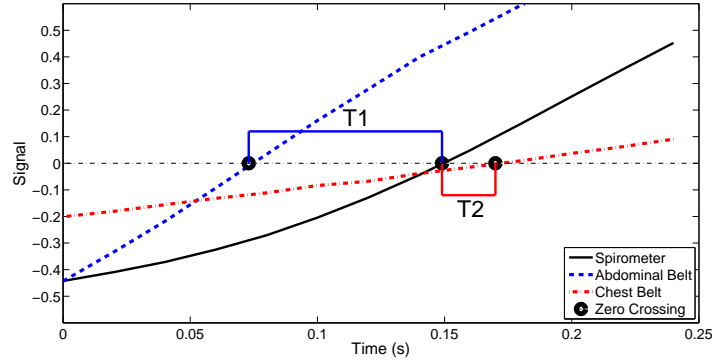
A mean time shift for a sensor across all participants of ± 0.1 s (2% of the length of a breath assuming a breathing rate of 12 breaths per minute [144]) was considered acceptable for real-time respiratory activity detection. Zero crossings that occurred outside 0.4 s of the start of exhalation, as detected by the spirometer, were deemed incorrect and ignored to avoid incorrect detections caused by noise.

Figure 4.3(a) shows a typical example of the sensor signals recorded during a full breath. Details of the respiratory effort belt and spirometer signals around the zero-crossing are depicted in Figure 4.3(b), which shows the time shift between the signals. In this example,

the abdominal belt signal precedes (a signal that precedes the spirometer signal will be denoted by a negative value of time shift) the spirometer signal by $T1 = 0.08$ s and the chest belt signal lags the spirometer signal by $T2 = 0.02$ s.



(a) All sensor signals



(b) Time shift

Figure 4.3: Example of sensor signals and the time shift between these signals and the spirometer. (a) shows an example of all of the sensor signals and their respective zero crossings during one full breath. (b) shows the time shift between the respiratory effort belt signals and the spirometer signal, where $T1$ is the time shift between the spirometer (black) and the abdominal (blue) belt signal and $T2$ is the time shift between the spirometer and the chest (red) belt signal.

4.3.4 Support Vector Machine

From pre-processed data (see Section 4.3.1) inhalations were detected, based on when the zero-crossings occurred (see previous section), and from each inhalation features were extracted (see below). The features from a subset of approximately 50 cough and 100 quiet breath inhalations, together with information indicating whether the data represented a quiet breath or a cough, were used to train an SVM on a participant by participant basis. After training, the SVM was used to classify all of the breaths recorded from that participant, and not used to train the SVM, as either a quiet breath or a cough, again using features extracted from each inhalation. The classification structure is shown in Figure 4.4 and explained in further detail in this section.

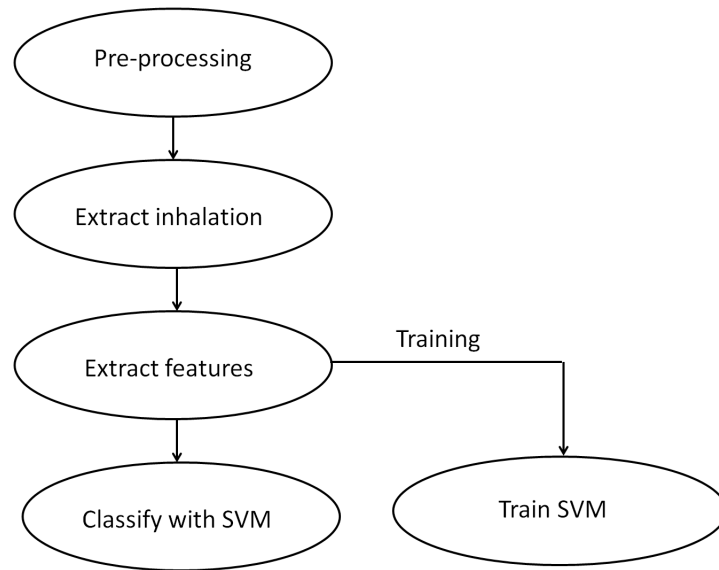


Figure 4.4: Classification structure. The classification algorithm firstly pre-processes all data and then extracts the inhalations and features from all data sets. The algorithm can then be used to either train the Support Vector Machine (SVM), or can use a trained SVM to classify respiratory activity.

4.3.4.1 Feature Extraction

Twenty one features (listed below), extracted from both the time and frequency domain, were calculated for each inhalation.

1. Length
2. Sum
3. Minimum value
4. Maximum value¹
5. Number of peaks
6. Mean
7. Mean magnitude (power spectral density) of Fast Fourier Transform (FFT)
8. Sum of magnitude (power spectral density) of FFT
9. Maximum magnitude (power spectral density) of FFT
10. Minimum magnitude (power spectral density) of FFT
11. Sum of magnitude (power spectral density) of FFT, divided by signal length
12. Index of minimum value
13. Mean gradient (Equation (4.1))
14. Minimum gradient (Equation (4.1))
15. Maximum gradient (Equation (4.1))
16. Sum of gradient (Equation (4.1))
17. Cross correlation with a quiet breath (Equation (4.2))

¹If using continuous sampling the maximum value of inhalation would be zero. Due to the discrete sampling technique employed, this was not the case. As quiet breaths have a smaller inhalation amplitude than coughs, the maximum sampled value of a quiet breath is likely to be closer to zero than the maximum sampled value of a cough

18. Cross correlation with a cough (Equation (4.2))
 19. Mean of autocorrelation (Equation (4.3))
 20. Maximum value of autocorrelation (Equation (4.3))
 21. Minimum value of autocorrelation (Equation (4.3))
- The gradient, Δs , was calculated using Equation (4.1).

$$\Delta s = s(i) - s(i - 1) \quad (4.1)$$

Δs is the difference between the value of the current data point, $s(i)$, and the previous data point, $s(i - 1)$.

Cross correlation, $c(t)$, between the measured signal, $y(k)$, and a reference breath, $x(k)$, was calculated using the equation used by Gollee *et al.* [72], shown in Equation (4.2). The reference breath, $x(k)$, was the mean of either all of the quiet breaths or all of the coughs collected from all participants during session one.

$$c(t) = \frac{\sum_{i=1}^N x(i)y(t - N + i)}{\sqrt{\sum_{i=1}^N x^2(i) \sum_{i=1}^N y^2(t - N + i)}} \quad (4.2)$$

$c(t)$ is defined as the similarity between the measured signal, $y(k)$, and the reference signal, $x(k)$, where the measured signal has a length of N sample points. The reference signal has a length of t sample points and i denotes the sample point being compared. If $c(t)$ is one, both samples are identical. If $c(t)$ is minus one both samples are identical, but have a phase difference of 180 degrees. A value of zero indicates that the signals are not correlated.

Autocorrelation, $a(t)$, was calculated using Equation (4.3).

$$a(t) = \sum_{k=1}^N \sum_{i=1}^N x(i)x(k + i - 1) \quad (4.3)$$

$a(t)$ is a comparison of a signal, x , of length N , at time point (i) , with the same signal at every other time point $(k + i - 1)$.

Examples of some of the quiet breath and cough features extracted from the time domain of the chest belt signal are shown in Figure 4.5.

To evaluate whether combining the signals from more than one sensor provided a better classification performance, the features from the respiratory effort belts positioned around the chest and the abdomen were combined, providing a total of 42 feature values.

4.3.4.2 Classification

Peak Expiratory Flow Peak Expiratory Flow (PEF), the maximum flow rate during exhalation (recorded with the spirometer), is greater for a cough than for a quiet breath. Therefore, PEF was used offline to label each inhalation as a quiet breath or a cough. The

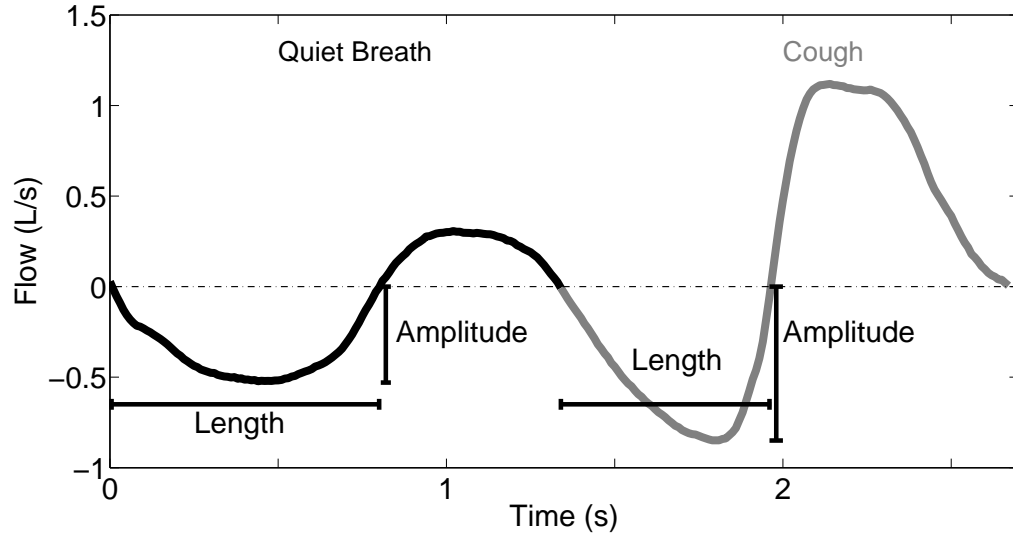


Figure 4.5: Respiratory flow signal recorded using a respiratory effort belt positioned around the chest. An example of the signal recorded during a cough and a quiet breath, in addition to example features extracted from these two breath types, is shown.

threshold for a breath to be deemed a cough was a PEF of 0.1 L/s greater than the maximum expiratory flow recorded during any of the quiet breaths recorded from that participant. This threshold was set on a participant by participant basis and provided a sensitivity of 100 percent. The labelled data was used to train the SVM and to allow the performance of the SVM to be assessed. Note that a real-time classification must be made at the end of each inhalation. For this reason PEF data, which is based on exhalation, would not be available for online classification in real-time.

Support Vector Machine The signals from the respiratory effort belts positioned around the abdomen and the chest, as well as a combination of these signals, were used to construct SVMs for each participant. The signal from the spirometer was used to create a baseline SVM with which the classification performance using the different non-intrusive sensor signals could be compared. To test the robustness of the SVMs a simple cross validation method was used. The SVMs were trained on a participant by participant basis using the data collected from session one (*Train 1*), session two (*Train 2*) and the first 50 percent of the data recorded from each session (*Mix*). This training data contained approximately 50 coughs and 100 quiet breaths.

The feature values, and a label denoting whether each breath was a quiet breath or a cough, were used to train the SVM model. Training was performed using a model developed from the MATLAB Bioinformatics Toolbox (Version 3.5), which was used to find the combination of features that separated the data in higher dimensional space by as large a margin, also known as a gap, as possible (see Section 2.4.4.4 for further explanation). When using an SVM data can be separated linearly, using a linear kernel, or non-linearly using a Radial

Basis Function (RBF) kernel. Therefore, an SVM was created using both kernel types. The strength of the soft margin (see Section 2.4.4.4 for further explanation) is controlled within this SVM model using a variable called ‘boxconstraint’. For both kernel types boxconstraint was varied offline between 1×10^{-5} and 1×10^5 , in steps of 1×10^1 , and the value of boxconstraint that achieved the highest combination of quiet breath and cough sensitivity was evaluated on a participant by participant basis for both kernel types.

4.3.4.3 Classification Performance

To evaluate the performance of the SVMs the data collected during the sessions that was not used to train the SVMs was classified as either a quiet breath or a cough, using the previously trained SVMs. For each breath type the classification sensitivity, Se , was calculated. Se is defined as the percentage of the number of breaths that were correctly classified as that breath type, N_y^i , over the total number of breaths that should have been classified as that breath type, N_t^i , where i denotes the breath type (c =cough, q =quiet breath).

$$Se^i = \frac{N_y^i}{N_t^i} \times 100 \quad (4.4)$$

Sensitivity of one breath type alone is not a suitable parameter to evaluate a classifier: for example, if every breath was classified as a cough this would lead to 100 percent cough classification sensitivity, even though all quiet breaths had been incorrectly classified as coughs, as false positives are not accounted for [149]. In the general case, *specificity* can be used to include the effect of false positive detection. In this case where only two classes are to be distinguished, the cough classification sensitivity is equal to the quiet breath classification specificity and vice versa.

As previously stated, it is believed that a greater stimulation intensity is required to generate an effective cough compared to a quiet breath [72]. Therefore, incorrect classification of a quiet breath as a cough would lead to a higher stimulation intensity than necessary being applied, with the breath said to be over stimulated. While this is not dangerous, as this higher stimulation intensity is safely being used to stimulate a cough, it may be less comfortable for the user as the greater stimulation intensity may lead to the recruitment of more pain receptors. It was agreed with clinical colleagues that in the context of an AFES system a high quiet breath sensitivity, which would lead to less quiet breaths being incorrectly over stimulated as coughs, was more important than a high cough sensitivity, which would lead to less coughs being incorrectly under stimulated as quiet breaths. It was agreed that a quiet breath sensitivity of greater than 95 percent was clinically suitable, as this would result in only one out of 20 quiet breaths being incorrectly stimulated as a cough, or approximately one quiet breath per 100 seconds of use (assuming a breathing rate of 12 breaths per minute [144]). A cough sensitivity of greater than 90 percent, which would lead to one in every 10 coughs being under stimulated, was also deemed to be clinically acceptable.

4.3.5 Statistical Analysis

A Shapiro-Wilk test was performed to test for normality of the feature values during both quiet breathing and coughing. A Pearson product-moment Correlation Coefficient (PCC) was calculated to ascertain whether quiet breaths and coughs and stimulated and unstimulated breaths were linearly correlated. A Wilcoxon signed-rank test was used to test for a statistically significant difference (p-value less than 0.05) between: quiet breath and cough feature values for each participant; the stimulated and unstimulated feature values for each participant; the classification performance between each of the non-intrusive sensors and the spirometer and the classification performance when classifying only stimulated or unstimulated breaths.

4.4 Results

The signals from the accelerometers and nasal/oral thermocouple could not be used for analysis. This was mainly attributed to poor data collection protocol and is discussed in further detail in Section 4.5. Therefore, this results section will only include data collected from the respiratory effort belts and spirometer.

4.4.1 Statistical Testing

The results of a Shapiro-Wilk test showed that for the spirometer all of the 210 (100%) quiet breath feature values and 174 (82.9%) of the cough feature values were not normally distributed (21 features for each of the 10 participants). This confirmed the use of a non-parametric test for significance testing. The PCC between quiet breathing and coughing was found to be 0.79, and the PCC between stimulated and unstimulated breaths was found to be 0.98, indicating a strong linear correlation between both sets of variables. Non-parametric distribution and high linear dependence between variables advocated the use of a Wilcoxon signed-rank test for significance testing.

4.4.2 Time Shift

Table 4.1 shows the mean time shift between the respiratory effort belt and spirometer signals at the start of exhalation (positive zero crossing). This value is calculated for each participant from all (approximately 300) breaths recorded from that participant, and then averaged over all participants.

The signal from the belt positioned around the abdomen was used to detect the start of exhalation 0.01 s before the spirometer, while the signal from the belt positioned around the chest was used to detect the start of exhalation 0.04 s after the spirometer. The signal from both of the belts could be used to detect the start of exhalation within 0.1 s of the spirometer signal.

Table 4.1: Time shift (mean \pm standard deviation) between the respiratory effort belt and spirometer signals at the start of exhalation for 10 participants. The time shift for each participant is calculated from approximately 300 breaths.

Sensor	Time Shift (s)
Chest Belt	0.04 \pm 0.12
Abdominal Belt	-0.01 \pm 0.12

4.4.3 Feature Selection

Of the 21 features (see Section 4.3.4.1) extracted from the various sensor signals, the number of features that had a statistically significantly different median for a quiet breath and cough for all 10 participants is shown in Table 4.2. The median of the feature values for each participant was calculated from the features of around 100 coughs and 200 quiet breaths.

Table 4.2: Number of features extracted from the spirometer, chest belt and abdominal belt signals that had a statistically significantly different median for quiet breathing and coughing for all 10 participants.

Sensor	Number of features
Spirometer	21
Chest Belt	18
Abdominal Belt	13

The median of all 21 features extracted from the spirometer signal was found to be statistically significantly different for a quiet breath and cough for all 10 participants. This advocated the use of these features within an SVM. For both the chest and abdominal belt over half of the features had a median that was statistically significantly different for a cough and a quiet breath. A list of the features that were found to have a statistically significantly different median for quiet breathing and coughing for each sensor can be found in Appendix A, Table A.1.

To find the effect of stimulation on the feature values, the number of features that had statistically significantly different medians for stimulated and unstimulated breaths, for all 10 participants, is shown in Table 4.3. Again the median was calculated from around 100 coughs and 200 quiet breaths for each participant.

It was found that the signals from the respiratory effort belts had a very low number of features that had a statistically significantly different median for stimulated and unstimulated breaths. A list of the features that were found to have a statistically significantly different median for stimulated and unstimulated breaths for each sensor can be found in Appendix A, Table A.2.

Table 4.3: Number of features extracted from the spirometer, chest belt and abdominal belt signals that had a statistically significantly different median for stimulated and unstimulated breaths for all 10 participants.

Sensor	Total no. of features
Spirometer	9
Chest Belt	1
Abdominal Belt	3

4.4.4 Classification

Boxplots showing the quiet breath and cough classification sensitivities achieved with the 10 participants when using the different sensors and training methods outlined in Section 4.3.4.2 are shown in Figure 4.6. The SVMs were trained on a participant by participant basis and evaluated using the data, collected over the two sessions, which was not used to train the classifier (approximately 50 coughs and 100 quiet breaths). Training was performed using a linear kernel and a boxconstraint value of 0.1.

The classification sensitivities achieved when training the SVM with data collected at both session one and two (*Mix*) provided the best combination of high cough and quiet breath classification sensitivities for all sensors. The cough classification sensitivity achieved using the signal from the abdominal belt and training with the data collected at session one (*Train 1*), was the only non-intrusive sensor that provided a cough classification sensitivity that was statistically significantly inferior to that achieved using the signal from the spirometer. The signal from the spirometer provided the highest quiet breath sensitivity, with this sensitivity found to be statistically significantly greater than that achieved using all but one of the non-intrusive sensor and training data combinations (chest belt and *Train 2*). The inter-quartile range of the quiet breathing sensitivity using the spirometer signal was consistently small, whereas the inter-quartile range was larger when using the signal from the non-intrusive sensors. The inter-quartile range of the cough sensitivity was generally larger than for quiet breathing, with minimal sensitivity as low as 50 percent. It should also be noted that when performing quiet breath classification using the chest belt and *Train1* there was one outlier, which had a classification sensitivity of 57 percent. This is believed to be due to non optimal training methods, detailed further in the discussion.

The classification performance that could be achieved using either a linear or RBF kernel was investigated, with a boxconstraint value of 0.1 and 1 found to provide the highest classification performance for these two kernel types respectively. The classification performance obtained when optimising the boxconstraint value on a participant by participant basis was also evaluated. The mean classification sensitivity achieved when training the SVM with the first 50 percent of the data recorded from session one and session two (*Mix*) (found to provide the best combination of high cough and quiet breath classification sensitivity as shown in

Figure 4.6) on a participant by participant basis and classifying the data not used to train the classifier (approximately 50 coughs and 100 quiet breaths) is presented in Table 4.4. The classification sensitivity achieved using *Train1* and *Train2* is presented in Appendix A.

Table 4.4: Mean percentage quiet breath (q) and cough (c) sensitivity (Se) (\pm standard deviation) achieved using the signals from the respiratory effort belts placed around the abdomen (abdo) and the chest, a combination of respiratory effort belt signals and the signal from a spirometer (spiro). The SVM was trained for each participant using a mix of the first 50% of the data recorded from session one and session two (*Mix*). Classification was performed on the data not used to train the SVM using: a linear kernel with a boxconstraint value of 0.1, a linear kernel with an optimised (opti) box constraint value for each participant, an RBF kernel with a boxconstraint value of one and an an RBF kernel with an optimised boxconstraint value for each participant. * indicates statistically significantly different from spirometer when using the same training data and † indicates statistically significantly different from results achieved using a linear kernel and box constraint of 0.1.

Sensor	Linear & 0.1		Linear & opti		RBF & 1		RBF & opti	
	Se^c (%)	Se^q (%)	Se^c (%)	Se^q (%)	Se^c (%)	Se^q (%)	Se^c (%)	Se^q (%)
Spiro	90.7 ± 7.6	98.9 ± 1.6	93.0 ± 5.7	98.9 ± 1.6	92.2 ± 9.6	91.8 † ± 5.3	96.2 † ± 3.9	90.9 † ± 6.4
Chest Belt	92.9 ± 4.9	96.1* ± 4.2	93.4 ± 5.3	96.8* ± 3.7	91.6 † ± 11.8	86.7 ± 3.8	90.6 † ± 11.7	90.0 ± 2.4
Both Belts	92.0 ± 6.0	91.5* ± 7.9	92.1 ± 6.0	91.6* ± 7.8	- -	- -	- -	- -
Abdo Belt	83.1 ± 14.6	89.4* ± 5.3	84.5 ± 12.9	91.5* ± 4.6	62.9* † ± 27.7	92.0 ± 5.3	82.3* † ± 11.1	83.6 † ± 11.2

Due to problems believed to be associated with over classification, the combined belt signals could not be evaluated with an RBF kernel. This issue is discussed in further detail in Section 4.5. The use of a linear kernel with a boxconstraint value optimised for each participant resulted in a slight (generally less than two percent) increase in the cough and quiet breath classification sensitivity. For the spirometer and chest belt the use of an RBF kernel led to a large (statistically significant in the case of the spirometer) decrease in quiet breath sensitivity, whether the value of boxconstraint was optimised or not, compared to when using a linear kernel. Similar trends were observed when using *Train1* and *Train2*.

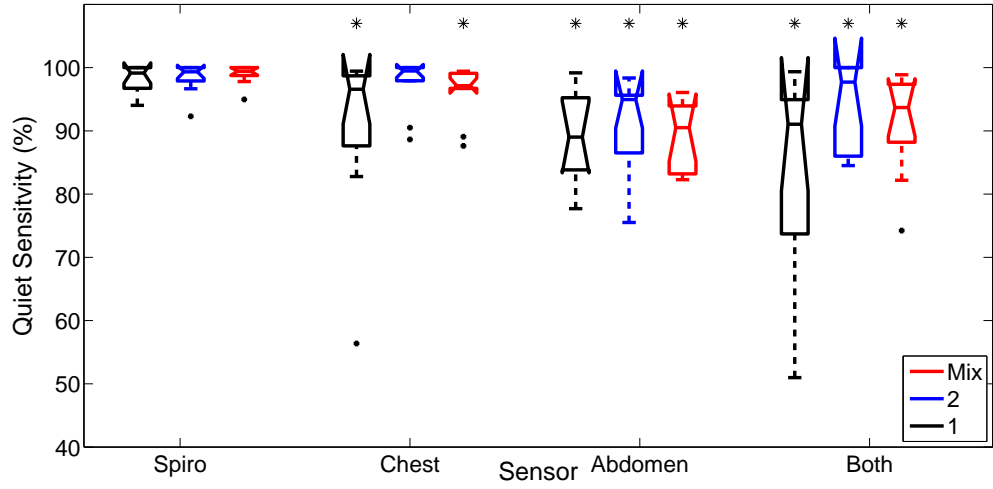
To assess the impact of AFES on classification performance, the classification sensitivity achieved when training with the same three training methods and classifying only stimulated or unstimulated breaths was investigated. The mean sensitivity achieved when training with the first 50 percent of the data recorded from session one and session two (*Mix*) and when classifying only stimulated or unstimulated breaths that were not used to train the SVM is shown in Table 4.5. The classification sensitivity achieved using *Train1* and *Train2* is

presented in Appendix A.

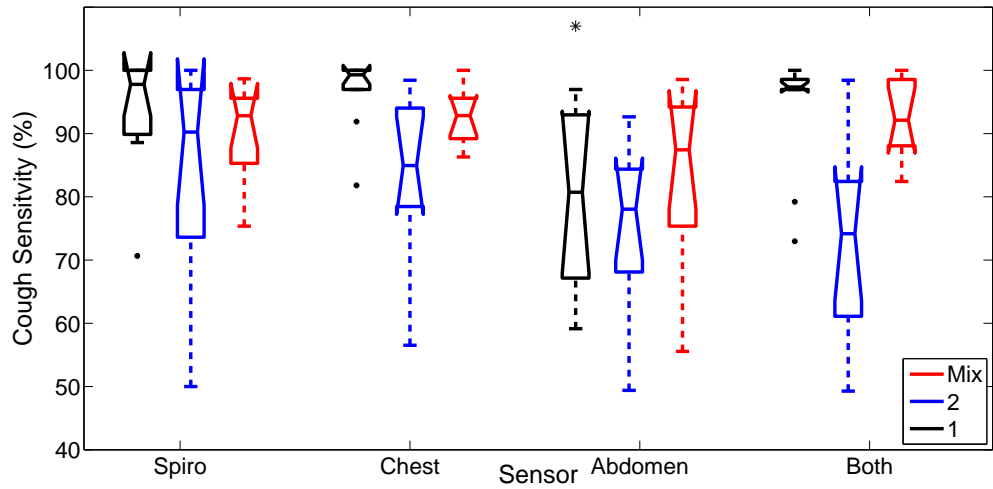
Table 4.5: Mean percentage cough (c) and quiet breath (q) sensitivity (Se) (\pm standard deviation) of stimulated (stim) and unstimulated (unstim) breaths using the signals from respiratory effort belts placed around the abdomen and the chest, a combination of these signals, and the signal from a spirometer. The SVM was trained for each participant using a mix of the first 50% of the data recorded from session one and session two (Mix). Classification was performed on the second 50% of the data recorded from session one and session two using a linear kernel and a boxconstraint value of 0.1.

Sensor	Stim Se^c (%)	Unstim Se^c (%)	Stim Se^q (%)	Unstim Se^q (%)
Spirometer	91.7 ± 7.6	89.7 ± 7.3	98.9 ± 2.0	98.7 ± 1.9
Chest Belt	93.0 ± 6.3	93.3 ± 6.0	95.9 ± 4.9	96.0 ± 4.0
Both Belts	90.1 ± 7.8	90.7 ± 9.3	89.9 ± 8.5	91.4 ± 8.6
Abdominal Belt	81.7 ± 17.1	84.8 ± 14.1	88.2 ± 7.2	91.2 ± 6.6

It was found that the classification performance was not statistically significantly different when classifying only stimulated or unstimulated breaths for any of the sensors. Similar trends were observed when using *Train1* and *Train2*.



(a) Quiet breathing sensitivity



(b) Cough sensitivity

Figure 4.6: Boxplots showing the classification sensitivities for different sensors and training data sets. Each box shows the median together with the inter-quartile range, with outliers marked by a black dot. (a) shows the median quiet breath sensitivity and inter-quartile range for the spirometer and respiratory effort belts when trained for each participant using: 1) all the data collected from that participant during session one (black), 2) all the data collected from that participant during session two (blue), *Mix* the first 50% of the data recorded from session one and session two (red). A linear kernel and a boxconstraint value of 0.1 were used to train the SVM, with classification performed on the data collected at the two sessions which was not used to train the classifier. (b) shows the cough sensitivity for the same sensors using the same training data. * indicates statistically significantly different from spirometer when using the same training data.

4.5 Discussion

In this chapter the signals from non-intrusive sensors were used to automatically detect and classify respiratory activity with minimal user intervention. The results show that a non-intrusive respiratory effort belt positioned around the chest can be used for the real-time detection and classification of respiratory activity, with an acceptable classification performance compared to that achieved using the signal from an intrusive spirometer. This suggests that a respiratory effort belt positioned around the chest, together with an SVM classification algorithm, can be used to detect and classify respiratory activity in the context of an automatic AFES system.

4.5.1 Timing

The abdominal muscles are active only during exhalation. Therefore, it is desirable to only apply AFES during this time, while avoiding the early application of stimulation which may curtail an inhalation. The signal from a spirometer, which is usually coupled with an intrusive facemask, has previously been used to detect respiratory activity, allowing AFES to be applied at the correct point in the respiratory cycle [72, 120, 121]. For a non-intrusive sensor to be suitable to detect respiratory activity in real-time it must have as small a time shift compared to the spirometer signal as possible, allowing accurate detection of the start of exhalation. The signal from a non-intrusive respiratory effort belt, positioned around the chest or the abdomen, was found to have a time shift of less than 0.05 s (1% of the length of a breath assuming a breathing rate of 12 breaths per minute [144]) compared to the signal from a spirometer. To perform the time shift analysis breaths that had a time shift of greater than 0.4 s were ignored in case of noise. It was found that for the chest belt signal, which had a larger time shift than the abdominal belt, the mean time shift plus three standard deviations was exactly 0.4 s, justifying this 0.4 s window. These results indicate that respiratory effort belts positioned around the chest or abdomen are suitable for the real-time detection of respiratory activity.

4.5.2 Classification Performance

To create a stand alone AFES device capable of differentiating between quiet breathing and coughing the signal from the input sensor must have features that differ for the two breath types. In this study 21 features were identified from the time and frequency domain of an inhalation, with the signal from the spirometer found to have a statistically significantly different median for a quiet breath and cough for all 21 features. This validated the use of these features for the classification of respiratory activity. It was also found that the use of AFES did not have a statistically significant impact on the feature values of the respiratory effort belts positioned around the chest and the abdomen, with one and three features having statistically significant medians for stimulated and unstimulated breaths for all 10 participants respectively. This allowed all breaths of the same type, stimulated or not, to be combined

into one data set for training purposes.

McCaughey and Gollee [131] used the signal from an intrusive spirometer as the input to a maximum likelihood classification algorithm, which was capable of differentiating between quiet breathing and coughing. This algorithm required a high degree of manual intervention, with the operator selecting the optimum features for classification based on each participant's training data. Here, the manual assignment of features was replaced with automatic feature selection and classification using an SVM. It was found that for all sensors the highest combination of quiet breath and cough classification sensitivities was achieved when training the SVM with a mixture of data collected at session one and two (*Mix*). Using this training method a non-intrusive respiratory effort belt positioned around the chest was used to provide a cough classification sensitivity (92.9%), which was similar to that achieved using the signal from an intrusive spirometer (90.7%). Although the quiet breathing sensitivity of 96.1 percent, achieved using the signal from the chest belt and training with *Mix*, was found to be statistically significantly lower than that achieved using the signal from the spirometer (98.9%), it would result in only one breath every two minutes (assuming a breathing rate of 12 breaths per minute [144]) being classified incorrectly. This quiet breath classification performance was greater than the minimum clinically relevant quiet breath classification performance of 95 percent that was agreed with clinical colleagues (see Section 4.3.4.3). The classification performance achieved using the signal from the belt positioned around the abdomen, and a combination of the chest and abdominal belt signals, provided an inferior classification performance compared to that achieved using the spirometer, which was not deemed to be clinically suitable. As the stimulation intensity applied during a quiet breath is lower than that applied during a cough, it is more desirable to incorrectly stimulate coughs as quiet breaths, where a breath will be under stimulated, than quiet breaths as coughs, where a breath will be overstimulated. The cough sensitivity achieved with the chest belt and training the SVM with a mixture of the data collected at session one and two (*Mix*) of 92.9 percent was lower than the quiet breath sensitivity of 96.1 percent achieved using the same sensor and training methods. However, this sensitivity, which would result in approximately 1 in every 12 coughs being incorrectly under stimulated, was greater than the clinically relevant minimum cough classification performance of 90 percent that was deemed acceptable in the context of an AFES system. Therefore, these results suggest that a respiratory effort belt positioned around the chest, together with the SVM classification algorithm, can be used to classify breathing patterns in the context of an automatic AFES system.

To test the robustness of the classifier, the impact of training the classifier with data recorded on different days was investigated. While training with a mix of data recorded at two different sessions (*Mix*) provided the best combination of high quiet breath and high cough classification sensitivities (see Figure 4.6), for the spirometer and chest belt these classification sensitivities were not statistically significantly different to those achieved when training the SVM with the data collected at session one (*Train 1*). This suggests that, with further

refinement of the training protocol, only one training session per user may be required to train the SVM. The lack of impact of stimulation on classification performance was also demonstrated by the classification sensitivity not being statistically significantly different when classifying only stimulated or unstimulated breaths. This would allow the user to receive a mixture of stimulated and unstimulated breaths during the training/familiarisation session. Practically, this would give the user the opportunity to experience the sensation of stimulation while the classifier was being trained, saving valuable time in the clinical setting where patient contact time can be limited.

The classification sensitivities that could be achieved by training the SVM with a non-linear RBF kernel, as opposed to a linear kernel, was investigated. However, the use of an RBF kernel instead of a linear kernel led to a large, statistically significant, decrease in quiet breath sensitivity when using the spirometer or chest belt. In addition, an RBF kernel is computationally more expensive than a linear kernel [150]. Therefore, a linear kernel was deemed preferential for this system. The boxconstraint value controls the strength of the soft margin (*i.e* how many misclassifications are allowed in the training data). The effect of optimising the boxconstraint value offline, on a participant by participant basis, to provide the best combination of high quiet breath and cough classification sensitivity, was also investigated. While this led to small, non statistically significant, improvements in cough and quiet breath sensitivity, this optimisation on a participant by participant basis requires a high degree of operator input, making it unsuitable for a clinical setting. Therefore, a boxconstraint value of 0.1 and a linear kernel is suggested for all further developments of the SVM.

4.5.3 Limitations

An RBF kernel could not be used to classify the combined belt signals, although the use of this kernel with the individual signal from both belts did provide a suitable classification performance. With the combined signals it was observed that every breath that was in the training data was classified correctly, while every breath that was not in the training data was classified as a quiet breath. When using the combined signals the classifier was provided with 42 features, compared to just 21 for the single signals. If the number of features was reduced, classification performance improved. This indicated that when using the 42 features there was a problem with over fitting. Over fitting occurs when classification is memorised rather than learned and the model has poor generalisation, a problem commonly encountered when using an RBF kernel and a large number of input features [151]. When using the linear kernel the classification performance achieved using both belt signals was not found to be greater than that achieved using the chest belt signal alone, leading to the belief that this problem of over fitting when using both belt signals did not justify further exploration.

The signals from the accelerometers and nasal/oral thermocouple were not suitable for

analysis due to a large amount of signal noise, attributed to poor data collection protocols. The amplitude of both signals was small leading to a poor signal to noise ratio. Data was sampled at 50 Hz, rendering the removal of mains artefact (also at 50 Hz) very difficult from both signals. For the accelerometers, the magnitude of acceleration achieved by body movement was much greater than that achieved during respiration. As the participants were not instructed to remain still during each session, this body movement artefact added a large degree of noise to the signal. As people with tetraplegia are likely to have some form of paralysis below the level of injury, body movement may be less of an issue with this group, making the accelerometers a potentially suitable sensor for measuring their respiratory activity. While the inability to use the nasal/oral thermocouples was disappointing, Farre *et al.* suggest that they are only semiquantative and cannot be used to accurately measure respiratory flow [140], which would have made them unsuitable for classifying respiratory activity. The sampling of data at 50 Hz, along with participants being free to move, should be avoided if using these sensors in future studies.

4.5.4 Future Work

While the current classification performance achieved using the signal from the spirometer and chest belt was deemed acceptable, the range of classification sensitivities observed across the participants may be improved by optimising the selection of training data. This may provide a better representation of a quiet breath and cough on which to base the classification. This optimisation could take the form of selecting more and/or better features or further refinement of the classification algorithm. This may allow the generation of a ‘universal’ training data set that provides a high classification performance for all users, negating the need for a training session. The classifier presented here is only capable of assigning breaths into one of two classes, a quiet breath or a cough. The system developed by Gollee *et al.* [72] was able to mute stimulation for periods of unexpected activity, such as speaking. Development of the classification algorithm to utilise a hierarchy of SVMs, where one level decides whether a breath is valid for classification, and another classifies a valid breath as a quiet breath or a cough, would enable the introduction of a ‘zero class’ for all breaths that were not suitable for classification. This would allow stimulation to be muted in all unusual situations, further improving the usefulness of the system.

In future work, the classification algorithm should be tested with tetraplegic participants. As people with tetraplegia have a reduced PEF, the difference in the feature values between a quiet breath and cough may not be as distinct as with the able bodied population. This may cause a reduction in classification performance for this patient group. Additionally, people with tetraplegia often exhibit paradoxical breathing, where the chest and abdomen move in opposing motions to that expected [152, 153, 154]. It is not anticipated that paradoxical breathing will lead to a reduction in classification performance, as breath features, and hence a distinction between breath types, should remain (with a phase shift of 180 degrees). However, further tests with tetraplegic patients who exhibit paradoxical breathing would be required

to establish the suitability of the system for this patient group.

4.6 Conclusion

The signal from a non-intrusive respiratory effort belt positioned around the chest can be used to achieve real-time classification of respiratory activity, with an acceptable performance compared to that achieved using the signal from an intrusive spirometer.

Chapter 5

Detection of the Motor Points of the Abdominal Muscles

“Everything should be made as simple as possible, but not one bit simpler.”

Albert Einstein

5.1 Summary

It is widely known that the optimum muscle response to electrical stimulation occurs when stimulation is applied in close proximity to the muscle motor point. Despite this, Abdominal Functional Electrical Stimulation (AFES) studies continue to use a range of empirically derived electrode locations, with no consensus as to the optimum electrode location. In this study the feasibility of using Neuromuscular Electrical Stimulation (NMES) to locate the motor points of the Rectus Abdominis (RA) and External Oblique (EO) muscles, along with the repeatability and uniformity of these motor point positions, was investigated with 10 able bodied and five tetraplegic participants. The motor points of the RA and EO muscles were successfully located for all 15 participants. The position of these motor points was found to change little over time, but was posture dependent and found to vary between participants. It was also shown that NMES could be used to detect these motor point positions with an adequate repeatability. Implementation of this motor point detection technique should indicate the optimum electrode placement for AFES. Application of AFES at these motor points should help achieve the optimum muscle contraction, which should lead to the greatest improvement in respiratory function and allow for easier comparison of AFES studies.

5.2 Background

When using electrical stimulation the optimum muscle contraction is observed when stimulation is applied close to the motor point, the location where the motor branch of a nerve enters a muscle [51]. Studies have shown that placing the stimulating electrodes at the motor point maximises force output and minimises discomfort [52, 53]. Despite this, studies investigating the effectiveness of AFES to improve respiratory function continue to use a range of empirically derived electrode locations (outlined in Section 2.4.4.3). This lack of consistency in electrode placement, and hence muscle contraction, makes a comparison of AFES studies difficult.

While anatomical charts showing the location of the motor points for the limbs have long been available [155], less information is available about the motor points of the muscles of the abdominal wall. Bell *et al.* [156] studied the underlying anatomical structures at the sites where AFES is usually applied and found that there were significant differences in these structures between participants. Botter *et al.* [128] used NMES to identify the position of the motor points of muscles in the leg and showed that these motor point positions varied between participants. The location of the motor points of the abdominal muscles, how they vary between participants and whether they are time and posture dependent has not been investigated in detail. This information would be useful for optimising the electrode placement used for AFES.

The aims of this study were i) to assess the feasibility of using NMES to detect the position of

the motor points of the RA and EO muscles and to assess the repeatability of this technique, ii) to evaluate the intersubject uniformity of these motor point positions, and iii) to evaluate how the motor point locations depend on posture and whether they vary over time.

5.3 Methods

5.3.1 Participants

Ten able bodied (five males, five females, age 29.5 ± 7.9 years (mean \pm standard deviation) [range 24 : 40 years]) and five tetraplegic participants (demographics shown in Table 5.1) were recruited. The tetraplegic participants, who were inpatients at the Queen Elizabeth National Spinal Injuries Unit, Southern General Hospital, Glasgow, were able to breathe independently, but had no useful abdominal movement and associated reduced respiratory function. Ethical approval to conduct the study with the able bodied participants was granted by the University of Glasgow College of Science and Engineering ethics committee (Local Code: CSE00965), while for the tetraplegic participants approval was granted by the National Health Service West of Scotland Research Ethics Committee (Local Code: 13/WS/0002). All procedures conformed to the Declaration of Helsinki and all participants gave written informed consent.

Table 5.1: Tetraplegic participant demographics showing sex, age, injury level, American Spinal Injuries Association Impairment Scale (AIS) level (see Section 1.2.3.2) and time post injury at recruitment.

Participant	Sex	Age (years)	Injury level	AIS level	Time post injury (days)
1	M	77	C3/4	C	31
2	M	24	C5/6	A	52
3	M	32	C5	B	46
4	M	20	C5	C	29
5	M	24	C5/6	C	19

5.3.2 Motor Point Detection

A virtual line was taken superiorly from the highest point of the iliac crest (top of the hip bone) until reaching the costal margin, as shown in Figure 5.1, with this distance used as the reference measurement in the superior direction (yn). The lateral distance between the umbilicus and this virtual line was taken as the reference measure in the lateral direction (xn). Both measurements, performed on the right hand side of the body, were recorded using a measuring tape and assumed to remain fixed throughout each assessment. They were used to normalise motor point positions in the corresponding direction to allow intersubject comparison.

To locate the position of the motor points, a bar electrode (MLADDF30, ADInstruments, New Zealand), with 9 mm diameter electrode contacts and 3 cm spacing between the contacts,

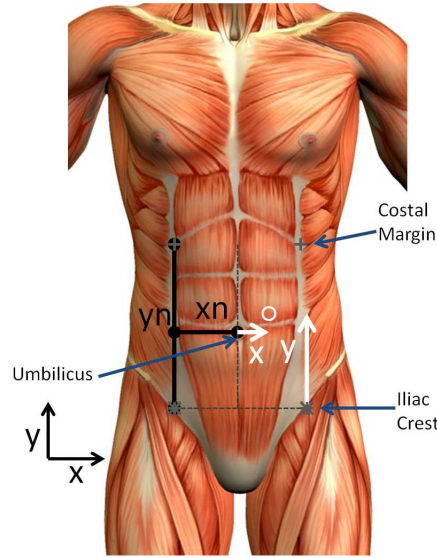


Figure 5.1: Diagram of reference and motor point position measurements. A virtual line was taken superiorly from the highest point of the iliac crest until reaching the costal margin. The superior length of this line (yn) and its lateral distance from the umbilicus (xn) were used as reference measurements for motor point positions. Motor point positions were normalised with respect to these distances. The white arrows illustrate the definition of the superior (y) and lateral (x) position of a motor point (represented by the white circle). Position of the iliac crest, costal margin and umbilicus is indicated by blue arrow.

was used. Electrolytic gel was applied to the electrode to enable the effective transfer of current from the electrode to the skin. To locate the position of the motor points of the EO muscles the bar electrode was positioned horizontally, slightly below the costal margin. The stimulation system outlined in Section 3.4.1 was used to apply single biphasic stimulation pulses, at a frequency of 0.5 Hz and a pulsewidth of 100 μ s, to initiate a twitch contraction. Stimulation current was adjusted on a participant by participant basis (20 to 60 mA for all participants) until a visible contraction of the muscle was achieved. The bar electrode was moved horizontally until the strongest muscle contraction was observed. This point of maximum contraction, determined both visually and from participant feedback, was recorded as the position of the motor point of the EO muscle. To locate the position of the motor point of the RA muscle the electrode was positioned vertically, approximately 3 cm horizontal of the umbilicus, and moved vertically and horizontally until the strongest muscle contraction was observed. This procedure was performed on both sides of the body, with the order in which each motor point was identified randomised for each participant. The position of each motor point was measured superiorly from the highest point of the iliac crest (y) and laterally from the umbilicus (x), as illustrated in Figure 5.1. This procedure took approximately two to five minutes. To reduce inter-operator variability the author of this thesis recorded the motor point positions for all participants. To further reduce experimental variability the same measuring tape, which had a resolution of approximately 0.25 cm, was used to measure all motor point positions.

Able bodied participants were asked to attend one assessment session (A1). Each participant was asked to sit in an upright position and the landmark measurements and motor point positions were recorded. Motor point position measurements were repeated after a rest period of approximately 30 minutes, during which time participants were free to move or walk about the room. The total duration of A1, summarised in Figure 5.2(a), was approximately one hour.

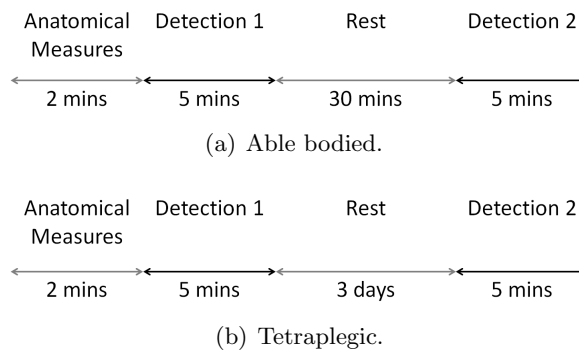


Figure 5.2: Experimental protocol showing periods of anatomical measurements, motor point recording and rest.

The same motor point detection procedure was used for the tetraplegic participants, but this was conducted at the participant's bedside, with participants in a supine position due to the acute stage of their Spinal Cord Injury (SCI). For these participants the procedure was repeated after three days, as shown in Figure 5.2(b), due to constraints on participant's time. Both measurements are referred to as assessment T1.

Five of the able bodied participants (three males, two females, age 28.8 ± 7.4 years (mean \pm standard deviation) [range 25 to 42 years]) were recalled after an 18 month period and the same motor point detection procedure performed, with the motor points being detected twice in both an upright seated (A2) and supine (A3) position. This 18 month period was chosen due to the realisation at this time of the need for the follow-up experiment, with only five participants recalled due to participant availability. The assessment procedures are summarised in Table 5.2.

Table 5.2: Summary of motor point detection assessment procedures for the able bodied and tetraplegic participants.

Assessment	Participant	Posture	Repeat	Time of assessment
A1	Able bodied	Seated	30 minutes	Baseline
A2	Able bodied	Seated	30 minutes	18 months after A1
A3	Able bodied	Supine	30 minutes	18 months after A1
T1	Tetraplegic	Supine	3 days	Baseline

5.3.3 Analysis and Outcome Measures

Motor point positions were analysed in the x direction as follows, equivalent calculations apply to motor point positions in the y direction. The absolute motor point position within an assessment session, measured in centimeters (cm), was calculated as the mean (\bar{x}^i) of the two measurements recorded at each assessment session from each (i) participant (x_1^i, x_2^i). The absolute motor point position was also normalised by the corresponding landmark distance xn^i (see Section 5.3.2), providing the mean normalised motor point position, \bar{x}_n^i , measured as a percentage of the corresponding landmark distance.

$$\bar{x}^i = \frac{x_1^i + x_2^i}{2} \quad (5.1)$$

$$\bar{x}_n^i = \frac{\bar{x}^i}{xn^i} \quad (5.2)$$

The standard deviation of the absolute difference between the two measurements within each assessment session for each participant was also calculated.

$$s_x = \sqrt{\frac{1}{N} \sum_{i=1}^N (x_1^i - x_2^i)^2} \quad (5.3)$$

(Note: $1/N$ is used to calculate s_x as real difference between these measurements is assumed to be zero).

The mean (\bar{X}) and standard deviation (s_X) of the motor point positions recorded at each assessment session for the N participants was calculated. This measurement is reported in absolute, measured in cm, and normalised (denoted by subscript n), measured as a percentage of the corresponding landmark distance, terms. A Student's independent t-test was used to test for a statistically significant difference (p-value less than 0.05) in the group motor point positions recorded at A1 and T1.

$$\bar{X} = \frac{1}{N} \sum_{i=1}^N \bar{x}^i \quad (5.4)$$

$$\bar{X}_n = \frac{1}{N} \sum_{i=1}^N \bar{x}_n^i \quad (5.5)$$

$$s_X = \sqrt{\frac{1}{N-1} \sum_{i=1}^N (\bar{x}^i - \bar{X})^2} \quad (5.6)$$

$$s_{X_n} = \sqrt{\frac{1}{N-1} \sum_{i=1}^N (\bar{x}_n^i - \bar{X}_n)^2} \quad (5.7)$$

The standard deviation of the normalised measurements, s_{X_n} , represents the intersubject uniformity of the motor point positions.

Assuming the real difference between a repeated measurement, taken from the same participant, is zero, the coefficient of repeatability (CoR) provides a range within which 95 percent of test-retest measurements will lie [157]. CoR was calculated to assess the repeatability of the two measurements recorded within the same assessment session (A) and is measured in cm.

$$CoR(A) = 1.96 \times s_x \quad (5.8)$$

CoR was also calculated to compare the motor point positions recorded at two different assessment sessions.

$$CoR(A1, A2) = 1.96 \times \sqrt{\frac{1}{N} \sum_{i=1}^N (\bar{x}_{A1}^i - \bar{x}_{A2}^i)^2} \text{ [cm]} \quad (5.9)$$

To assess the repeatability of using NMES to detect motor point position, the mean of the CoR calculated for the two motor point positions recorded from each participant at A1, A2, A3 and T1, using Equation 5.8, was used.

$$\overline{CoR} = \frac{1}{4} (CoR(A1) + CoR(A2) + CoR(A3) + CoR(T1)) \quad (5.10)$$

To evaluate the time and posture dependence of the motor point positions, Equation 5.9 was used to calculate the CoR for the motor point positions recorded at sessions (A1,A2) and (A2,A3).

5.4 Results

The mean of the reference measurements, yn and xn , recorded at the various assessment sessions are shown in Table 5.3.

The normalised locations of the motor points of the RA and EO muscles recorded at A1 and T1 are shown in Figure 5.3. Figure 5.3(a) depicts the motor points for each participant (taken as the mean of the two repeat measurements within each assessment session). Figure 5.3(b) shows the normalised motor point positions for each muscle, grouped by assessment session. While the median motor point positions of the EO muscles are in approximately the same normalised position for both the able bodied and tetraplegic participants, the range of the positions when measured superiorly from the iliac crest line was relatively large. For the RA muscles, the motor point positions for the two participant groups are different in both the lateral and superior directions. Also shown are the normalised locations of the umbilicus in the superior direction, which indicates that these also differ between both groups.

The mean (\pm standard deviation) motor point positions recorded at A1 and T1 are shown in Table 5.4 as both absolute and normalised measurements. It can be seen that the absolute motor point positions recorded at T1 were all statistically significantly different to the motor point positions recorded at A1 when measured from the iliac crest (\bar{Y}). However, when these

Table 5.3: Mean (\pm standard deviation) and range of reference measurements recorded in the vertical yn and horizontal direction xn for the 10 able bodied participants who took part in A1 and the five tetraplegic participants who took part in T1. Also shown is the mean (\pm standard deviation) of the reference measurements of the five able bodied participants who were recalled for a second assessment session, recorded at A1 and A2/3.

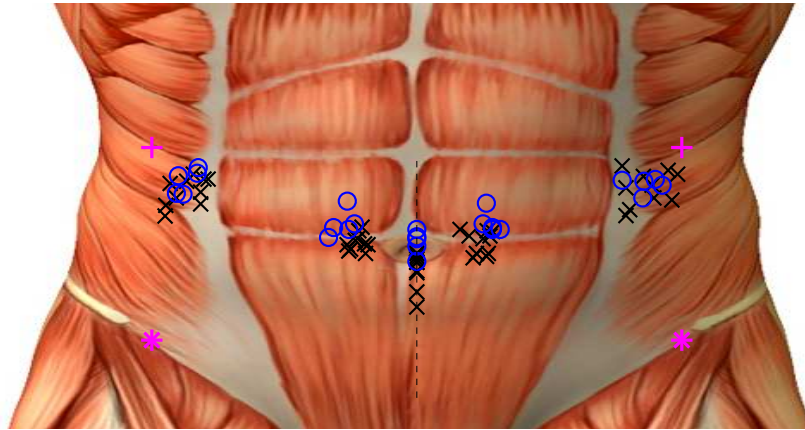
Assessment	Number of Participants	Measurement (cm)	Mean \pm std (cm)	Range
A1	10	yn	11.1 ± 2.3	9 – 16.5
		xn	18.0 ± 2.2	14 – 20
T1	5	yn	14.6 ± 4.7	12 – 23
		xn	17.1 ± 2.3	13.5 – 20
A1	5	yn	10.6 ± 0.5	10 – 11
		xn	18.2 ± 2.4	14 – 20
A2/3	5	yn	10.4 ± 0.5	10 – 11
		xn	17.7 ± 2.4	13.5 – 19

measurements were normalised to allow for more effective comparison between groups, \bar{Y}_n , only the motor points of the RA muscles were in a statistically significantly different position at T1 compared to A1. These motor points were found to be statistically significantly closer to the costal margin. The uniformity of these motor point positions, the standard deviation of the normalised positions, was found to range from 2.8 to 8.8 percent.

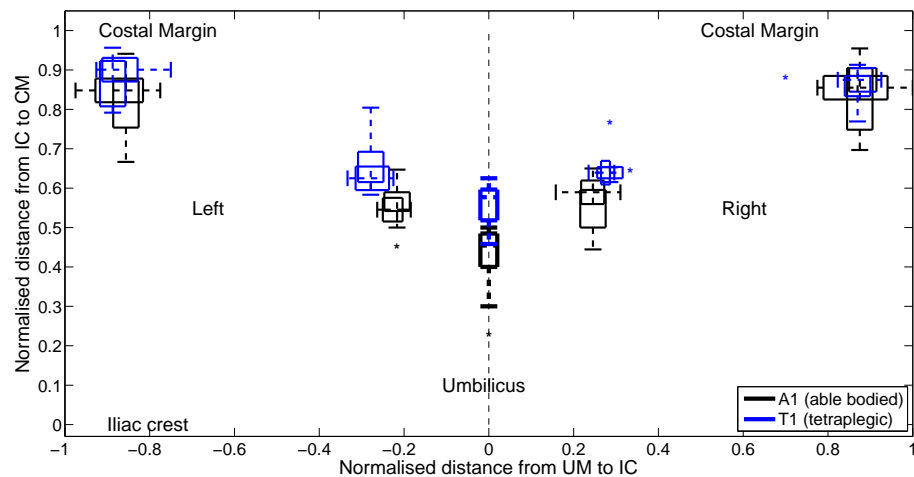
Table 5.4: Mean position and standard deviation (intersubject uniformity) of the position of the Rectus Abdominis (RA) and External Oblique (EO) motor points for assessment A1 (10 able bodied participants) and T1 (five tetraplegic participants). Results are expressed as absolute distances measured superiorly from the iliac crest (\bar{Y}) and laterally from the umbilicus (\bar{X}), and corresponding normalised distances with respect to the reference measurements (\bar{Y}_n and \bar{X}_n), \pm standard deviations s . * indicates mean of T1 is statistically significantly different to mean of A1.

Ass.	Muscle	$\bar{Y} \pm s_Y$ [cm]	$\bar{X} \pm s_X$ [cm]	$\bar{Y}_n \pm s_{Y_n}$ [%]	$\bar{X}_n \pm s_{X_n}$ [%]
A1	RA–Right	6.2 ± 1.1	4.3 ± 0.7	55.8 ± 6.1	24.1 ± 4.0
	RA–Left	6.2 ± 1.3	4.0 ± 0.7	55.8 ± 4.4	22.3 ± 2.8
	EO–Right	9.2 ± 1.4	15.6 ± 2.1	83.9 ± 8.8	86.9 ± 7.8
	EO–Left	9.1 ± 1.7	15.6 ± 2.3	82.3 ± 7.3	86.7 ± 6.3
T1	RA–Right	$9.9 \pm 4.3^*$	4.8 ± 0.5	$66.0 \pm 5.8^*$	28.0 ± 2.5
	RA–Left	$9.8 \pm 4.5^*$	4.8 ± 0.6	$65.4 \pm 7.1^*$	$28.1 \pm 4.1^*$
	EO–Right	$12.6 \pm 4.3^*$	14.7 ± 1.3	85.7 ± 4.0	86.2 ± 5.8
	EO–Left	$13.0 \pm 5.0^*$	14.8 ± 1.6	87.7 ± 6.3	86.9 ± 3.9

The mean (\pm standard deviation) motor point positions recorded from the five participants who took part in A1, A2 and A3 are shown in Table 5.4 as both absolute and normalised



(a) Normalised individual motor point positions recorded at A1 (black \times) and T1 (blue \circ). Also shown are the landmarks for the reference measurements (top of the iliac crest (purple $*$), corresponding point on the costal margin (purple $+$)).



(b) Group motor point positions (median and inter-quartile ranges), recorded at A1 (black) and T1 (blue), normalised with respect to the vertical distance from the Iliac Crest (IC) to the Costal Margin (CM) and the horizontal distance from the Umbilicus (UM) to the Iliac Crest.

Figure 5.3: Individual and group motor point position of the external oblique (outer left and right) and rectus abdominis (inner left and right) muscles of 10 able bodied (assessment A1, black symbols) and five tetraplegic (assessment T1, blue symbols) participants, with the position of the umbilicus shown on the midline. Motor point positions are normalised to the reference measurements shown in Figure 5.1.

measurements. It can be seen that the motor point positions recorded 18 months apart at A1 and A2 were very similar, with only the normalised position of the right EO muscle, when measured from the umbilicus (\bar{X}_n), being found to be statistically significantly different. However, when comparing the motor point position in an upright (A2) and supine position (A3) the absolute position of the motor points of the RA muscle on both sides of the body, and the EO muscle on the left side of the body, when measured from the iliac crest (\bar{Y}) were found to be statistically significantly different. Although the normalised motor point

positions of the RA were closer to the costal margin at A3 compared to A2 (*i.e.* a larger value of \bar{Y}_n) none of the normalised motor point positions were found to be statistically significantly different.

Table 5.5: Mean position and standard deviation of the position of the Rectus Abdominis (RA) and External Oblique (EO) motor points for assessment A1 (five able bodied participants) and A2 (18 months later) and A3 (supine). Results are expressed as absolute distances measured superiorly from the iliac crest (\bar{Y}) and laterally from the umbilicus (\bar{X}), and corresponding normalised distances with respect to the reference measurements (\bar{Y}_n and \bar{X}_n), \pm standard deviations s . * indicates mean of A2 is statistically significantly different to mean of A1, † indicates mean of A3 is statistically significantly different to mean of A2.

Ass.	Muscle	$\bar{Y} \pm s_Y$ [cm]	$\bar{X} \pm s_X$ [cm]	$\bar{Y}_n \pm s_{Y_n}$ [%]	$\bar{X}_n \pm s_{X_n}$ [%]
A1	RA–Right	6.0 \pm 0.8	4.0 \pm 0.7	56.1 \pm 6.8	22.6 \pm 5.1
	RA–Left	5.7 \pm 0.4	4.1 \pm 0.8	54.0 \pm 2.2	22.4 \pm 3.2
	EO–Right	9.1 \pm 0.9	15.0 \pm 2.2	85.6 \pm 8.4	82.2 \pm 4.8
	EO–Left	9.0 \pm 0.9	15.4 \pm 2.5	84.3 \pm 5.9	84.5 \pm 6.5
A2	RA–Right	6.1 \pm 0.7	3.8 \pm 0.4	58.2 \pm 6.8	21.7 \pm 3.1
	RA–Left	5.8 \pm 0.5	3.9 \pm 0.6	55.3 \pm 3.9	21.9 \pm 2.8
	EO–Right	8.8 \pm 0.6	15.6 \pm 2.0	84.4 \pm 8.2	88.2 \pm 1.3*
	EO–Left	8.6 \pm 0.3	15.6 \pm 1.8	82.4 \pm 4.8	88.2 \pm 5.3
A3	RA–Right	7.1 \pm 0.7 †	4.3 \pm 0.7	61.4 \pm 7.1	24.8 \pm 3.0
	RA–Left	6.9 \pm 0.6 †	3.7 \pm 0.5	59.4 \pm 7.3	21.7 \pm 3.1
	EO–Right	9.0 \pm 0.3	15.4 \pm 1.8	77.4 \pm 4.6	89.3 \pm 1.5
	EO–Left	9.0 \pm 0.2 †	15.1 \pm 1.8	77.9 \pm 4.7	87.6 \pm 1.5

Table 5.6 shows the mean CoR between the two measurements of motor point position recorded at all assessments (A1, T1, A2 and A3, \overline{CoR}) which provides a measure of the repeatability of the measurement technique. The repeatability of the motor point position over time was assessed by comparing motor point positions at assessments A1 and A2 ($CoR(A1, A2)$), which were performed 18 months apart, while the coefficient of repeatability between assessment A2 (seated) and A3 (supine) shows the influence of posture ($CoR(A2, A3)$) on motor point position. From \overline{CoR} it can be concluded that 95% of test-retest measurement differences would be less than 1.7 cm, with a similar CoR even after an 18 month period ($CoR(A1, A2)$). The CoR is greater if tests are performed with different postures ($CoR(A2, A3)$), indicating a dependence of motor point position on posture in particular for the RA muscle when measured in the superior direction (y).

Table 5.6: Mean coefficient of repeatability (\overline{CoR}) of the position of the motor points of the Rectus Abdominis (RA) and External Oblique (EO) muscles recorded 30 minutes apart for: 10 able bodied participants in seated position (A1); five able bodied participants after 18 months in seated position (A2); five able bodied participants after 18 months in supine position (A3) and three days apart for five tetraplegic participants in supine position (T1). Also shown is the mean CoR of the motor point positions recorded 18 months apart ($CoR(A1, A2)$) and in a seated and supine position ($CoR(A2, A3)$). Results are expressed as absolute distances measured superiorly from the iliac crest (y) and laterally from the umbilicus (x).

Muscle	\overline{CoR}		$CoR(A1, A2)$		$CoR(A2, A3)$	
	y [cm]	x [cm]	y [cm]	x [cm]	y [cm]	x [cm]
RA–Right	1.2	0.9	0.9	1.3	3.1	1.5
RA–Left	0.9	0.8	0.7	0.9	2.3	1.1
EO–Right	1.0	1.6	1.3	1.5	1.5	1.4
EO–Left	1.3	1.6	1.5	1.6	1.0	1.9

5.5 Discussion

In this chapter the feasibility of using NMES to detect the position of the motor points of the RA and EO muscles was demonstrated for the first time. Using a simple and quick procedure, these motor points were detected successfully in all 10 able bodied and five tetraplegic participants. A range of intersubject uniformities and an adequate intrasubject repeatability was demonstrated for these motor point positions when recorded at the same assessment session and after 18 months. Variations in posture resulted in a change of the position of the motor points of the RA muscle.

The results of this study suggest that the use of NMES can be easily adopted to reliably detect the position of the motor points of the abdominal muscles. As the abdominal muscles are often not included in standard motor point charts [155], and due to the adequate repeatability found here, it is suggested that this technique should be adopted as standard procedure for all future AFES studies.

5.5.1 Motor Point Position

When analysing the position of the motor points of muscles in the leg Botter *et al.* [128] developed criteria that allowed values of uniformity to be classed as ‘good’, ‘fair’ or ‘bad’. It was found that when classifying the intersubject uniformity of the motor point position measurements recorded at assessments A1 and T1 (see s_{X_n} and s_{Y_n} in Table 5.4), three were ‘good’, six were ‘fair’ and seven were ‘bad’. However, it should be noted that uniformity depends on how normalisation is performed. Botter *et al.* based their uniformity calculations on normalising the muscles by their estimated lengths, while in this study the locations are

normalised by anatomical reference measurements. Additionally, Botter *et al.* had a sample size of 53 participants, compared to the two groups of five tetraplegic and 10 able bodied participants in this study. This lower sample size inherently leads to a greater standard deviation and poorer uniformity. Nevertheless, the range of intersubject uniformity observed here suggests that the use of standard motor point locations may not be suitable for detecting the exact location of the motor points of the abdominal muscles, agreeing with the finding of Botter *et al.* for the muscles of the leg.

Bland and Altman [157] suggest the CoR as a technique to assess the test-retest repeatability of a method with a 95 percent confidence. In this study the largest CoR between the motor point positions recorded at A1, A2, A3 and T1 was 1.6 cm for the EO muscles and 1.2 cm for the RA muscles. This indicates that if the motor points of these muscles were to be detected twice, on 95 percent of occasions the difference between these measurements would be 1.6 cm or less. During the two measurements no restrictions were placed on participant movement, indicating that NMES can be used to detect the position of the motor points with good repeatability, even after time and activity.

When the positions of the motor points were detected 18 months apart the largest CoR was also 1.6 cm, indicating that the positions of the motor points remain relative constant over time. The electrodes typically used for AFES studies are approximately 5 cm long with a space of approximately 3 cm between the electrodes [71, 72]. This means that the CoR would fall within this electrode area and suggests that use of the motor point detection technique outlined here to locate the position of the motor points once for each individual, at the start of a course of AFES, would be adequate.

Placement of the stimulating electrodes at the motor points appeared to lead to a more effective muscle contraction compared to when using empirically derived electrode locations. The effect of this should be twofold. Firstly, this should lead to a greater benefit from using AFES which may, in turn, lead to a greater improvement in the respiratory function of the user and improve their quality of life. Secondly, it should ensure a consistent muscle contraction across AFES studies, making a comparison of such studies easier.

The motor points of the tetraplegic participants were detected in a supine position due to the acute stage of their SCI. For these participants the motor points of the RA muscle, when measured vertically from the iliac crest, were statistically significantly closer to the costal margin than for the able bodied participants (see \bar{Y}_n for RA in Table 5.4). This posture dependance of motor point position was further highlighted when the motor points of five of the able bodied participants were detected in both an upright and supine position. In these tests the absolute position of the motor points of the RA muscle were found to be statistically significantly (greater than 1 cm) closer to the costal margin in a supine position. Additionally, while the normalised positions were not statistically significantly different, they

were again closer to the costal margin in a supine position. The CoR between motor point positions detected in an upright and supine position was also found to be as large as 3.1 cm. This suggests that motor point positions are posture dependant and should be re-identified if posture changes occur.

5.5.2 Impact of Findings

The detection of the motor points of the abdominal muscles may be useful in the development of an AFES garment, which houses electrodes at a fixed location for a particular user. This garment could take the form of a belt with an array of buttons or velcro, with electrodes attached to the garment at the appropriate location to stimulate the motor points, detected using the technique outlined here. Such a garment would ensure that stimulation was applied at the same location at different training sessions, reducing intersession variability. The incorporation of a garment into an automatic AFES device, such as that discussed in Section 8.5, would further increase the usefulness of an AFES system.

Dyskinesia, a movement disorder causing involuntary muscle movements, has been reported to affect the abdominal muscles [158, 159, 160]. The application of Botulinum toxin A (BoTN-A) to a nerve to prevent it from functioning, known as nerve blocking, has been used to treat dyskinesia [161]. For effective nerve blocking BoTN-A should be applied at the motor point [162]. The detection of the motor points of the abdominal muscles using the methods outlined here may aid in the application of BoTN-A for treating dyskinesia and other movement disorders that cause spasm of the abdominal wall. Studies have shown that the use of NMES to train the abdominal muscles of able bodied participants can lead to improved muscle strength, endurance and appearance [163, 164]. This method of motor point detection may be beneficial to select the optimum electrode placement when using NMES for this use.

Anatomical investigations of the abdominal muscles [156] suggest that the RA and EO muscles have more than one motor point. In this study, the focus was to detect the location where the strongest contraction was observed. For two of the able bodied participants there appeared to be a second motor point of the RA muscle, located just below the costal margin. This motor point was not present in all participants, or could not be as easily detected as the other motor point positions reported here. One reason for this difficulty of detection may be that this motor point is located deeper than the other motor points. It is also possible that this motor point belonged to another muscle group, situated in close proximity to the RA muscle. While Langbein *et al.* [71] used an electrode position that may have stimulated this ‘second’ motor point of the RA muscle (see Figure 2.1(e)), the difficulty of detection found here suggests that the application of AFES at this point would not achieve an effective muscle contraction. The position of the motor points of the EO muscle reported here were the only motor points of this muscle detected.

5.5.3 Limitations

A potential limitation of this study was the accuracy with which the motor point positions could be measured. By using a traditional measuring tape the resolution was approximately 0.25 cm. This resolution may account for some of the CoR and uniformity values that were observed. One solution to this problem would be to use position markers in combination with an accurate position measurement system to measure the motor point positions. However, these devices tend to be large, making them impractical in an acute care setting. Additionally, the author measured all motor point positions to reduce inter-operator variability. To evaluate this inter-operator variability a second operator could have been used to detect all motor point positions. Finally, previous motor point detection studies have used a pen electrode to apply stimulation [52, 128]. In this study a bar electrode, which spreads stimulation over a larger surface area, was used to minimise user discomfort. This larger electrode size may have led to it being more difficult to accurately locate the position of a motor point. The low CoR observed in this study suggests that neither of these measurement inaccuracies had a major influence on accurately locating the position of the motor points.

5.6 Conclusion

This study has demonstrated for the first time the feasibility of using NMES to reliably detect the position of the motor points of the abdominal muscles in both the able bodied and tetraplegic population. While the position of the motor points of the RA and EO muscles change little over time, they were found to be posture dependent, and variations were observed between participants. The motor point detection procedure described in this study should enable the optimum AFES electrode location for each user to be identified, which if adopted as a standard technique for all AFES studies, would allow easier comparison of studies.

Chapter 6

Abdominal FES to Assist Ventilator Weaning in Tetraplegia

“Money does not represent such a value as men have placed upon it. All my money has been invested into experiments with which I have made new discoveries enabling mankind to have a little easier life.”

Nikola Tesla

6.1 Summary

Paralysis of the respiratory muscles, resulting from tetraplegia, leads to reduced respiratory function. This reduction in respiratory function causes many people with tetraplegia to require mechanical ventilation in the acute stage of injury. In a single participant case study documented in this chapter, the use of an Abdominal Functional Electrical Stimulation (AFES) training program was found to be a feasible technique to assist ventilator weaning with one chronic ventilator dependent tetraplegic participant. This study was the motivation for investigating the use of an AFES training program to assist ventilator weaning for the acute tetraplegic population in a larger clinical study. In this study the feasibility of using an AFES training program to improve respiratory function and assist weaning from mechanical ventilation was investigated with 10 acute ventilator dependant tetraplegics. Each participant was matched with a retrospective ventilator dependent control, based on injury level, age and sex, who had received no intervention. AFES was applied five times per week, on four alternate weeks, for between 20 and 40 minutes per day. Vital Capacity (V_C) and Tidal Volume (V_T) were measured at weekly assessment sessions, with weaning progress also recorded and compared to the retrospective controls. The application of AFES was associated with an acute increase in V_T and V_C . V_T and V_C increased throughout the study. Participants who received AFES training were found to wean from mechanical ventilation on average 11 days faster than their matched controls. The results of this study indicate that AFES is a feasible technique for improving the respiratory function of ventilator dependent acute tetraplegics, and that this technique may enable faster weaning from mechanical ventilation.

6.2 Introductory Case Study

A Spinal Cord Injury (SCI) can be classified by three distinct phases of recovery from injury, namely the acute, sub-acute and chronic phase. Acute SCI generally refers to the immediate post-injury period when there is continuing tissue damage and the patient is in spinal shock. This phase generally lasts for up to four weeks [19]. While the spinal cord undergoes a reparative process and there is continuing neurological recovery an SCI can be classified as sub-acute, with this phase typically beginning around four weeks after injury and continuing for three months. When neurological recovery has reached a plateau an SCI can be classified as chronic, which typically occurs approximately three months after injury [20]. Respiratory failure leads to some patients with tetraplegia requiring mechanical ventilation in the acute stage of injury. This respiratory failure is commonly caused by paralysis or severe impairment of the respiratory muscles, the neurological level of SCI ascending one or two levels because of bleeding or swelling in the area of the trauma (reducing function of respiratory muscles not originally affected by the SCI) and subsequent respiratory complications [47]. This use of mechanical ventilation reduces the patient's quality of life and costs the health care provider approximately an additional £1000 per ventilated day [27, 46].

While most of these patients will wean from mechanical ventilation within a number of weeks people with chronic tetraplegia who retain some diaphragm function can fail to wean from mechanical ventilation for a number of reasons, most notably as a result of frequent respiratory infections and complications [47, 122]. These patients continue to suffer a decrease in quality of life and an increased susceptibility to respiratory infections while reliant on mechanical ventilation [27, 84]. Therefore, a reduction in time spent dependent on mechanical ventilation will have benefits for both the patient and the health care provider.

A study by Lee *et al.* [122] demonstrated that an AFES training program could be used to assist ventilator weaning, the process of removing a patient from mechanical ventilation, for a ventilator dependent chronic tetraplegic patient who retained some diaphragm function (see Section 2.4.4.2). However, no larger studies investigating the effectiveness of AFES to assist ventilator weaning for patients who retain some diaphragm function have been conducted¹. Before conducting a larger study investigating the effectiveness of AFES to assist ventilator weaning at the Queen Elizabeth National Spinal Injuries Unit (QENSIU), the feasibility of conducting such a study with the tetraplegic population had to be determined.

In Chapter 4 the use of a respiratory effort belt positioned around the chest to automatically detect and classify respiratory activity was demonstrated. Clinically, this technology would allow AFES to be applied in synchrony with the user's respiratory activity, reducing reliance on a trained operator. In Chapter 5 the use of Neuromuscular Electrical Stimulation (NMES) to detect the abdominal muscle motor points of able bodied and tetraplegic patients was also demonstrated. By placing AFES at the motor points found using this technique the optimum muscle contraction should be achieved. It is hypothesised that this will lead to the greatest improvement in respiratory function. However, the suitability of these two methods for use with the ventilator dependent tetraplegic population required to be tested before being implemented in any larger study.

The three aims of this case study were to assess the feasibility of using i) an AFES training program to assist ventilator weaning for the tetraplegic population, ii) a respiratory effort belt to automatically apply stimulation in synchrony with the respiratory activity of tetraplegic patients and iii) NMES to detect the motor points of the abdominal muscles of ventilator dependent tetraplegic patients.

6.2.1 Methods

One chronic tetraplegic participant (female, age 76 years, C5, AIS A, 13 weeks post injury), who was an inpatient at the QENSIU and had difficulty weaning from mechanical ventilation, despite retaining some diaphragm function, was recruited for this study. Due to the need for mechanical ventilation the participant had a tracheostomy, which was present throughout

¹Patients who do not retain diaphragm function will not be able to breathe independently of mechanical ventilation or diaphragm pacing

the study duration.

Five times weekly training sessions, used to strengthen the abdominal muscles, were performed for 20 minutes per day for three weeks. AFES was applied using the system described in Section 3.4.1. During training sessions stimulation was applied in synchrony with the participant's respiratory activity using the signal from the respiratory effort belt positioned around the abdomen (automatic stimulation methods are explained in more detail in Section 3.4.3). The rectus abdominis and external oblique muscles were stimulated using electrodes positioned at the motor points of these muscles, found using the protocol outlined in Chapter 5. A stimulation current of 100 mA was used to achieve a visible muscle contraction at all training sessions. Stimulation pulsewidth was varied between 100 and 500 μs within each session to account for muscle fatigue. Where possible, training sessions were performed while the participant was disconnected from mechanical ventilation, with the participant reconnected to mechanical ventilation during the session if their oxygen saturation level decreased below 92 percent. If the participant could not be disconnected from mechanical ventilation, as was the case at the first three sessions and at the fourth and fifth training sessions in week two, training was performed while the participant remained connected to mechanical ventilation throughout.

The participant's V_C was measured at the first and final training session by disconnecting the participant from mechanical ventilation and asking them to inhale as deeply as possible and exhale fully. No verbal encouragement was provided during the exhalation. The maximum value of three successful attempts, judged to be such using the protocol described in Section 3.2, which lay within 0.15 L/s of another attempt was taken to be the participant's V_C . This measurement was made using a standard medical spirometer (Wright Respirometer, Ferraris Development and Engineering Company Limited, London, United Kingdom) which was attached to the participant's tracheostomy tube. While this is a rudimentary way of recording V_C , only the feasibility of measuring the respiratory function of ventilator dependent tetraplegic patients, rather than the effect of this technique on respiratory function, was assessed within this study.

The daily time spent breathing without the support of mechanical ventilation was used to give a primitive indication as to the effectiveness of the intervention.

6.2.2 Results

The training session on day four of week two of AFES training was missed due to the patient being unwell, resulting in a compliance rate to training sessions of 93 percent. The participant had spent 14 weeks without being able to breathe independently of mechanical ventilation before AFES training commenced. Figure 6.1 shows the daily time spent breathing without mechanical ventilation during the AFES training period.

After three days of AFES training the participant was able to breathe independently of

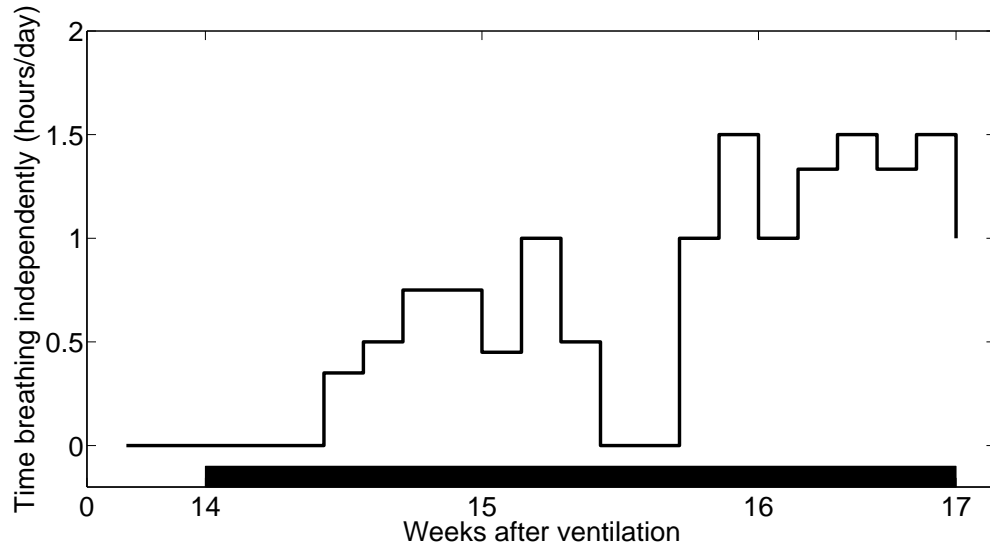


Figure 6.1: Time spent per day breathing without mechanical ventilation for one chronic tetraplegic participant during a three week AFES training program. Solid black line along bottom of plot indicates AFES training period.

mechanical ventilation for the first time. The participant being unwell during the middle part of week two of participation (15 weeks after ventilation) resulted in them not spending any time breathing without the assistance of mechanical ventilation for three days. Despite this, the time spent breathing independently of mechanical ventilation increased from zero hours per day to one and a half hours per day during the AFES training period. Importantly, on the final day of the second week of the study this one and a half hours was achieved in three separate 30 minute sessions, while in the final week of the study this one and a half hours was achieved in one session. The participant's V_C was 60 mL before the AFES training period and 160 mL after, indicating that AFES training may be improving respiratory function.

6.2.3 Discussion

People with chronic tetraplegia who retain some diaphragm function can fail to wean from mechanical ventilation for a number of reasons, most notably as a result of frequent respiratory infections and complications [47, 122]. The aim of this case study was to evaluate the feasibility and effectiveness of using an AFES training program to assist ventilator weaning for the chronic tetraplegic population who retain some diaphragm function. The feasibility of this intervention was demonstrated by the adequate muscle contraction observed in this case study and the 93 percent compliance to the training sessions achieved. The results show that time spent breathing independently of ventilation and V_C increased during the AFES training period. This suggests that AFES training can be used to assist chronic tetraplegic patients to wean from mechanical ventilation, agreeing with the findings of Lee *et al.* [122].

While the participant was only able to achieve 90 minutes of ventilator free breathing during the study duration, this had some significant effects on the participant's quality of life.

Firstly, the ability to breathe independently of mechanical ventilation removed some of the participant's fear of disconnection from mechanical ventilation, a common problem for ventilator dependant tetraplegics [97]. Breathing independently of ventilation also improved the participant's feeling of wellbeing and made their transfer from a supine position to a wheelchair easier. All of these factors combined to give the participant a perceived improvement in quality of life.

This case study also provided the opportunity to test some of the technology developed in the previous two chapters of this thesis in a clinical setting. In Chapter 4 the use of a respiratory effort belt positioned around the chest was shown to be suitable for detecting and classifying respiratory activity. In this case study no classification of respiratory activity was made as it was assumed the participant would only be taking quiet breaths and not coughing. However, it was initially assumed that the signal from a respiratory effort belt positioned around the chest would allow AFES to be applied in synchrony with the respiratory activity of the participant. By conducting this study it was found that the respiratory effort belt used to measure respiratory activity had to be placed around the abdomen. This was because many tetraplegics require a halo or back brace to stabilise their SCI, limiting access to their chest. It was established that the signal from a respiratory effort belt positioned around the abdomen could be used to apply AFES in synchrony with the patient's respiratory activity. In Chapter 5 the use of NMES to detect the abdominal muscle motor points was demonstrated with 10 able bodied and five tetraplegic participants. In this case study the use of NMES to detect the motor points of ventilator dependent tetraplegic participants was also shown to be feasible.

To confirm the effectiveness of AFES to improve respiratory function and assist ventilator weaning for chronic tetraplegic participants who retain some diaphragm function a randomised clinical study is required, with the weaning progress of the intervention group compared to that of a control group who did not receive AFES training. However, due to the small number of chronic tetraplegic participants who retain diaphragm function but have difficulty weaning from mechanical ventilation at the QENSIU (one or two per year) it was not possible to conduct such a study within this thesis. A multicentre study may enable the recruitment of a sufficient number of participants to evaluate the effectiveness of this intervention.

However, this case study does demonstrate that AFES can feasibly be used to assist ventilator weaning for the ventilator dependent tetraplegic population.

Clinical Study

6.3 Background

Poor respiratory function often leads to people with tetraplegia requiring mechanical ventilation during the acute stage of injury (see Section 2.3.1). Reliance on mechanical ventilation reduces a patient's quality of life, leaves them more susceptible to respiratory infection and places a cost burden on the local health care provider [27, 46]. An improvement in respiratory function that leads to a reduction in time spent dependant on mechanical ventilation will have significant benefits.

The use of AFES has been shown to improve the respiratory function of people with chronic (greater than three months post injury) and sub-acute (between four weeks and three months post injury) tetraplegia. The acute effect of AFES, the immediate improvement in respiratory function achieved by applying stimulation, has been observed in a number of studies (see Section 2.4.4.1). Langbein *et al.* [71] found that the application of AFES led to a mean 13 percent increase in the Forced Vital Capacity (FVC) of 10 spinal cord injured participants. This increase in FVC was slightly less than the 17 percent increase observed by Lee *et al.* [122] with one chronic tetraplegic participant. Gollee *et al.* [72] found that the application of AFES led to an increase in Tidal Volume (V_T) of between nine and 71 percent for four chronic tetraplegic participants. Kandare *et al.* [123] used AFES to support ventilation in three chronic tetraplegic participants who had no respiratory drive and were unable to breathe independently. However, they found that the V_T generated with AFES was approximately 25 percent less than that generated with the support of mechanical ventilation. Additionally, the repeated application of AFES, known as AFES training, has been shown to lead to a longitudinal increase in respiratory function. McBain *et al.* [73] found a mean longitudinal increase in V_C of 20 percent after a six week AFES training program with 15 chronic tetraplegic participants, while McLachlan *et al.* [70] found FVC to increase by a mean of 0.36 L after a three week AFES training program with 12 sub-acute and chronic tetraplegic participants. Therefore, these studies indicate that AFES can be used to improve the respiratory function of chronic and sub-acute tetraplegic participants.

A study by Lee *et al.* [122] demonstrated that an AFES training program could be used to improve respiratory function and assist ventilator weaning for a ventilator dependent chronic tetraplegic patient who retained some diaphragm function (see Section 2.4.4.2). The feasibility of conducting a clinical study using this method at the QENSIU was demonstrated by the case study outlined above. For tetraplegic patients who require mechanical ventilation in the acute stage of injury, the need for mechanical ventilation reduces quality of life and has a cost implication for the health care provider. Additionally, both the acute stage of tetraplegia and the need for mechanical ventilation are associated with a high susceptibility

to respiratory complications (see Section 2.4), largely attributed to poor respiratory function. Therefore, an early intervention that improves respiratory function would not only reduce this patient groups susceptibility to respiratory complications, it would also improve quality of life and reduce the cost to the health care provider. Routsis *et al.* [125] applied FES to the leg muscles of acute ventilator dependant patients, hypothesising that FES could beneficially improve muscle functional status. They found that in addition to improving muscle function, FES training led to these patients weaning from mechanical ventilation statistically significantly faster than patients who did not receive FES. In this chapter the use of AFES to improve respiratory function and assist ventilator weaning for the acute (less than four weeks post injury) ventilator dependent tetraplegic population is investigated.

To evaluate the effectiveness of this intervention it is necessary to estimate when weaning has occurred and the time to wean if the intervention had not been applied. Current understanding is that injury level, age and sex are the best indicators of weaning time for this patient group, with weaning being deemed to be successful after a period of 24 hours or seven days of ventilator free breathing (see Section 2.3.1).

The aim of this study was to evaluate the feasibility and effectiveness of using an AFES training program to improve respiratory function and assist ventilator weaning in acute tetraplegia.

6.4 Methods

Ten tetraplegic participants, who were inpatients on the high dependency ward of the QENSIU, were recruited for this study. The study was approved by the National Health Service Scotland A research ethics committee (Local Code: 11/SS/0098). Patients were unable to give written informed consent due to high levels of sedation needed in the early stages of mechanical ventilation. Written informed consent was obtained from each participant's welfare guardian. Consent was later sought from the participant if they were deemed to have regained capacity within the study duration. All experimental procedures conformed to the Declaration of Helsinki.

Participants were recruited according to the following inclusion and exclusion criteria.

Inclusion criteria:

1. Men or women over 16 years of age;
2. Acute tetraplegia (patients less than four weeks post injury);
3. Reduced respiratory function requiring mechanical ventilation;
4. Good visual response to surface electrical stimulation of the abdominal muscles, suggesting that lower motor neurons are intact.

Exclusion criteria:

1. Under 16 years of age;

2. Female participants who are pregnant;
3. Significant history of autonomic dysreflexia;
4. No visual response to surface electrical stimulation of the abdominal muscles, suggesting that lower motor neurons are not intact;
5. Unstable chest or abdominal injury;
6. Bulbar dysfunction.

Participants were recruited for this study by consultants at the QENSIU, based on the inclusion and exclusion criteria provided above. However, the ultimate decision for inclusion was based on the clinical judgement of the consultant.

All participants in this study had a tracheostomy tube fitted to allow mechanical ventilation to be applied via the trachea. This tracheostomy tube was removed within one week of weaning from mechanical ventilation for all participants.

Each participant was matched with a retrospective control participant, obtained from records of previous patients at the QENSIU, based on injury level, age (within five years) and sex. Each of these control participants required mechanical ventilation in the acute stage of injury. All matching of intervention and control participants was performed by a consultant at the QENSIU, based on the criteria outlined above. However, due to the relatively small number of retrospective controls available at the QENSIU, a limited number of suitable controls were available to the consultants. Therefore, matching was based on the clinical judgement of the consultant, with the author not made aware of the detailed process.

The daily time that each of these participants spent breathing without the support of mechanical ventilation, along with the point at which they weaned from mechanical ventilation, was retrieved from their patient notes by a consultant at the QENSIU. This allowed a comparison of the time to wean from mechanical ventilation between the intervention and control participants. The demographics of both the intervention and control participants are shown in Table 6.1. It should be noted that Participant 5 was a non-responder to electrical stimulation, whereby the applications of AFES achieved no muscle contraction. Therefore this participant did not complete the study and as such no control participant was sought for Participant 5.

6.4.1 Protocol

Each participant took part in AFES training sessions five times per week, on four alternate weeks, with the total duration of participation eight weeks. The participant's progress was monitored at weekly assessment sessions. An effort was made to perform all procedures at the same time of day and all procedures were performed at the participant's bedside with the participant in a supine position.

Table 6.1: Intervention and control participant (part') demographics showing sex, age, injury level, American Spinal Injuries Association Impairment Scale (AIS) level (see Section 1.2.3.2), weight and time post injury at recruitment.

Part'	Sex	Age (years)	Intervention				Time Post injury (days)	Control			
			Injury level	AIS level	Weight (kg)			Sex	Age (years)	Injury level	AIS level
1	F	42	C4	A	50	20	M	34	C5	A	
2	M	63	C3/4	A	70	39	M	63	C3	C	
3	M	38	C4	C	78	24	M	35	C5	A	
4	M	53	C4	B	81	29	F	58	C4	A	
5	M	44	C0/5	A	90	24	-	-	-	-	
6	M	77	C3/4	C	76	10	M	78	C4	A	
7	M	74	C6/7	C	82	43	M	73	C6	A	
8	M	24	C5/6	A	80	11	M	25	C5	B	
9	M	32	C5	B	95	11	M	32	C5	A	
10	F	35	C7	A	75	11	M	32	C5	A	

6.4.1.1 Training Session

Five weekly training sessions, used to strengthen the abdominal muscles, were performed for 20 minutes per day in week one, 30 minutes per day in week three and 40 per day minutes in weeks five and seven as shown in Figure 6.2. The cycle of one week with AFES training and one week without was used to provide an indication of the effectiveness of the intervention for improving respiratory function in the short term.

Recruitment

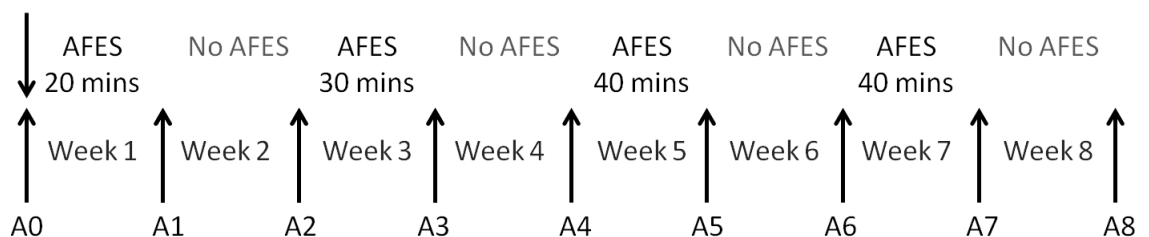


Figure 6.2: Study timeline showing weeks with and without AFES training, training duration and assessment sessions (A.).

Based on previous research [86, 165, 166] participants were expected to go through four distinct phases before successfully weaning from mechanical ventilation. These phases are summarised in Table 6.2. This table shows that participants were initially fully ventilator dependent and unable to breathe without the support of mechanical ventilation. However, it should be noted that during this time participants could be disconnected from mechanical ventilation for short periods of time, during which they would show some respiratory

activity. As the study progressed these participants were disconnected from the ventilator and encouraged to breathe independently from mechanical ventilation for increasing periods of time, a process refereed to as ventilator weaning.

Table 6.2: Expected phases of weaning, adapted from [86, 165, 166]

Phase 1. Participants unable to breathe independently of mechanical ventilation	Participants are not be able to breathe independently of mechanical ventilation. Levels of ventilatory support are reduced throughout this period.
Phase 2. Participants disconnected from mechanical ventilation and Spontaneous Breathing Trials (SBTs) begin	Participants are only able to undertake SBTs (see Section 2.3.1) for a short period of time before oxygen saturation level (SaPO_2) falls below 92 percent. During this time participants struggle to actively participate or follow instructions. All breaths at Vital Capacity (V_C).
Phase 3. Participants become accustomed to breathing without ventilator support	Duration of each SBT can be increased before SaPO_2 falls below 92 percent. All breaths continue to be at V_C until respiratory function begins to improve.
Phase 4. Participants can actively participate while disconnected from mechanical ventilation	Duration of SBTs increases beyond one hour. Respiratory function improves to a level where Tidal Volume (V_T) of a normal breath is below V_C . Participants are able to actively take deeper breaths to V_C when requested. Duration of SBTs continues to increase until participant is freed from mechanical ventilation.

While participants were not able to breathe independently of mechanical ventilation, represented by Phase 1 in Table 6.2, AFES was applied while the participants remained connected to mechanical ventilation. As weaning progressed through the stages outlined in Phases 2 to 4 of Table 6.2, Spontaneous Breathing Trials (SBTs) (see Section 2.3.1) began, during which participants were encouraged to breathe independently of mechanical ventilation for increasing periods of time. During this time AFES was applied while participants were disconnected from mechanical ventilation. However, during SBTs the participant's oxygen saturation level (SaPO_2) was monitored and recorded every minute. If SaPO_2 decreased below 92 percent participants were immediately reconnected to mechanical ventilation until SaPO_2 returned to baseline, at which point they were once again disconnected from mechanical ventilation. AFES was applied throughout this process. AFES training sessions continued throughout the eight weeks even if the participant successfully weaned from mechanical ventilation within the study duration as it was believed that, even if the participant had weaned from mechanical ventilation, AFES training would continue to improve their respiratory function.

6.4.1.2 Assessment Session

Before the study commenced, and at the end of each week, an assessment session was conducted as shown in Figure 6.2. Before the first assessment session commenced the stimulation current required to achieve a visible contraction of the rectus abdominis and external oblique muscles was established. During each assessment session V_T and V_C were measured, with and without AFES, using the protocol described in Section 3.2. To record V_C participants were asked to inhale to maximum lung capacity and exhale as fully as possible. This manoeuvre was repeated up to five times, both with and without AFES, to form one run. V_T was then recorded by measuring six minutes of normal relaxed breathing, both with and without the support of AFES, separated by a rest period of approximately two minutes. This provided approximately 75 stimulated and unstimulated breaths, the mean of which was denoted as the V_T . A second run of V_C manoeuvres was then performed after a rest period of approximately two minutes. This resulted in each assessment session providing up to 10 stimulated and unstimulated V_C manoeuvres. The maximum of these manoeuvres, which was within 0.15 L of another breath, was taken as the V_C . Whether stimulation was applied during the first or second set of five V_C manoeuvres within each run was randomised for each participant at each session. During all measurements of V_C participants were asked to inhale and exhale as deeply as possible. However, no verbal encouragement was provided during the exhalation. It should be noted that V_C was recorded rather than FVC as, at early assessment sessions, participants could not always exhale as ‘forcibly as possible’ due to sedation levels and poor respiratory muscle coordination. However, as explained in Section 1.4.2, there is very little difference between the values of V_C and FVC. A plot demonstrating a V_T and V_C measurement, recorded using a spirometer with Participant 10 at the final assessment session (A8), is shown in Figure 6.3.

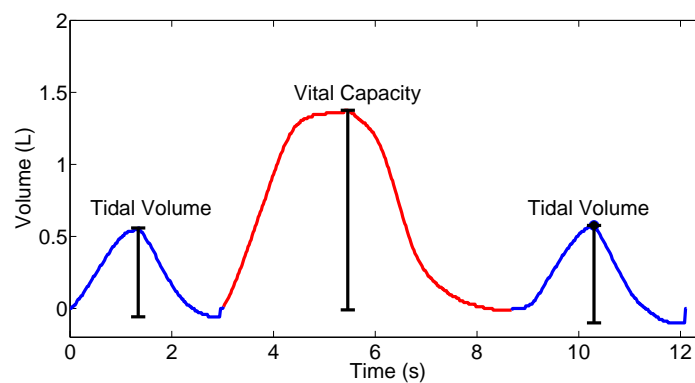


Figure 6.3: A respiratory volume trace recorded from Participant 10 using a spirometer at the final assessment session. A positive gradient represents an inhalation and a negative gradient represents an exhalation. The participant was asked to undertake a Vital Capacity (V_C) manoeuvre (shown in red), preceded and proceeded by a regular breath (shown in blue). V_C was calculated from the total volume during the exhalation phase of the V_C manoeuvre, found to be approximately 1.3 L. Tidal Volume (V_T) was calculated from the total volume during the exhalation phase of the normal breaths, found to be approximately 0.6 L.

In cases where participants were unable to actively participate, most commonly due to high levels of sedation in the early stages of the study, their V_T , which was assumed to also be their V_C at this acute stage of injury, was recorded from the output of the mechanical ventilator. During the first (A0) and second (A1) assessment with Participant 1, and the first (A0) assessment with Participant 6, V_T was calculated as the mean of six breaths recorded from the ventilator, while V_C was calculated as the maximum of these breaths. All other participants were able to actively participate at all assessment sessions.

In cases where the participant was unable to sustain respiration without the support of mechanical ventilation for extended periods of time their SaPO_2 was monitored and recorded during every minute of the assessment session. If SaPO_2 decreased below 92 percent participants were immediately reconnected to mechanical ventilation until SaPO_2 returned to baseline, at which point they were once again disconnected from mechanical ventilation and the assessment session resumed. If SaPO_2 fell below 92 percent during a period where V_T was measured only breaths measured before the participant was reconnected to mechanical ventilation were used for analysis. This only occurred at the first assessment session (A0) for Participant 10, where 20 stimulated and unstimulated quiet breaths were used to calculate V_T .

6.4.1.3 Time to Wean

Each participant's weaning progress was monitored on a daily basis throughout the course of the study. Two measures were used to determine whether weaning had been successful: i) Short term weaned - Participant able to breathe independently of mechanical ventilation for 24 hours and ii) Long term weaned - Participant able to breathe independently of mechanical ventilation for seven days.

The duration of SBTs conducted within the QENSIU is recorded in the patient's notes. This allowed a comparison of the time spent breathing without mechanical ventilation to be made between the intervention and control participants. The time for the control participants to wean from mechanical ventilation was retrospectively assessed over the first 100 days of ventilation, used as an approximate comparison with the maximum possible participation in the intervention arm of this study (assuming intervention participant is recruited approximately four weeks after initial ventilation and takes part in the full eight week AFES training program).

6.4.2 Equipment

During training sessions the participant's respiratory activity was detected using a respiratory effort belt positioned around the abdomen, while during assessment sessions respiratory activity was recorded using a spirometer, with both of these methods described in Section 3.3. The reliability of a respiratory effort belt to detect respiratory activity was shown in Chapter 4

(Note no classification of different kinds of respiratory activity was performed in this study as all breaths were assumed to be quiet breaths). In initial assessment sessions the spirometer was connected to the participant's tracheostomy tube. If the tracheostomy cuff, a balloon which directs all air out of the tracheostomy tube, was removed during the study duration the spirometer was connected to a mouthpiece. The participant was asked to breathe through this mouthpiece while their tracheostomy tube (if still present) was capped to avoid air leakage. If the participant was unable to breath without the support of mechanical ventilation a pressure sensor was connected in line with the expiratory limb of the ventilator and used to measure the ventilator's, and in turn the participant's, respiratory activity. Data was collected and pre-processed using the methods described in Section 3.3.

6.4.2.1 Stimulation System

AFES was applied using the stimulation system described in Section 3.4.1. During training sessions stimulation was applied in synchrony with the participant's respiratory activity using the signal from the respiratory effort belt positioned around the abdomen. During assessment sessions stimulation was applied in synchrony with the participant's respiratory activity using the signal from the spirometer. If the participant was unable to breath without the support of mechanical ventilation stimulation was applied in synchrony with the ventilator using the signal from the pressure sensor (automatic stimulation methods are explained in more detail in Section 3.4.3). The rectus abdominis and external oblique muscles were stimulated using electrodes positioned at the motor points of these muscles, found using the protocol outlined in Chapter 5. The stimulation currents required to achieve a visible muscle contraction of these muscles at the pre-study assessment (with a pulsewidth of $100\ \mu s$), was used at all subsequent sessions, and is shown for each participant in Table 6.3. The same stimulation current was used throughout the eight weeks of participation, with the response to stimulation not appearing to change over this period. Stimulation pulsewidth was varied between 100 and $500\ \mu s$ within each session to account for muscle fatigue. It should be noted that as Participant 5 was a non-responder to AFES, no stimulation currents could achieve a contraction with this participant.

6.4.3 Analysis and Outcome Measures

The primary outcomes measures of this study are the time to wean from mechanical ventilation and respiratory function. Respiratory function was quantified by V_T and V_C . Individual results recorded from each participant are presented as V_T and V_C measured in litres (L). Group results are normalised by weight and are presented as weight corrected tidal volume (V_T/kg) and weight corrected vital capacity (V_C/kg) [39, 38, 42]. V_T/kg and V_C/kg are measured in milliliters per kilogram (mL/kg).

The variability of time to wean from mechanical ventilation in the tetraplegic population, coupled with the fact that the quantitative effectiveness of the intervention was largely

Table 6.3: Stimulation currents, in mA, used to achieve a visible contraction of the External Oblique (EO) and Rectus Abdominis (RA) muscle groups for each participant.

Participant	Right EO mA	Left EO mA	Right RA mA	Left RA mA
1	70	70	50	50
2	30	50	40	40
3	50	50	30	30
4	60	60	50	60
5	<i>N/A</i>	<i>N/A</i>	<i>N/A</i>	<i>N/A</i>
6	50	50	50	50
7	100	105	100	105
8	60	50	50	50
9	75	70	55	75
10	75	75	75	65

unknown in this patient group, made it difficult to reliably estimate the required sample size for this study. The target number of participants was determined by an estimate of the available patient population at the QENSIU who would be eligible for this study.

Participant 7 did not complete the final assessment session (A8) due to poor health. Therefore, their results recorded during the previous assessment session were used for group analysis. The eight assessment sessions conducted with Participant 7, and the nine assessment sessions conducted with the eight other participants, provided 80 individual assessment sessions. These 80 assessment sessions, conducted with nine participants, allowed 71 longitudinal comparisons (*i.e.* A0 compared to A1).

The stimulated and unstimulated V_T /kg data recorded during the nine assessment sessions with each of the nine participants were grouped into two data sets and tested for normality using the Shapiro-Wilk test. The same process was performed on the V_C /kg data. Based on the results of these tests a Kruskal-Wallis test was used to test for statistically significant longitudinal changes in stimulated and unstimulated V_T /kg and V_C /kg and for a statistically significant difference in the stimulated and unstimulated V_T , V_T /kg and V_C /kg recorded at each assessment session. In the case of significance (p-value of less than 0.05), post hoc multiple comparisons were performed using the Tukey-Kramer honest significant difference test to identify statistically significantly different pairs. As V_C is the maximum value recorded at an assessment session, it was not possible to test for a statistically significant difference between the stimulated and unstimulated V_C recorded at any individual assessment session, or for longitudinal changes in stimulated and unstimulated V_C for each participant. On the advice of clinical colleagues, it was agreed that an increase in V_C of 200 mL was regarded as clinically significant.

The mean time for the intervention and control participants to achieve 24 hours (short term weaned) and seven days (long term weaned) of ventilator free breathing, from the date of initial ventilation, was compared for statistical significance using an independent Student's t-test.

6.5 Results

At the initial assessment session (A0) conducted with Participant 5 it was observed that this participant did not respond to AFES. Despite this AFES was applied daily for three further days with varying electrode positions and stimulation intensities. AFES was then applied on a weekly basis throughout the eight weeks of participation, however no response to AFES was observed at any of these sessions. As described in Section 6.6.2, it was later discovered that this participant had suffered Lower Motor Neuron (LMN) damage. Due to this lack of response to AFES Participant 5's data was not included in the analysis.

A Shapiro-Wilk test showed that both the stimulated and unstimulated V_T /kg data sets, which contained approximately 3000 breaths each, and the stimulated and unstimulated V_C /kg data sets, which contained 81 breaths each, were not normally distributed, validating the use of a non-parametric test for significance testing.

In the remainder of this section improvements in respiratory function, assessed by measuring V_T and V_C , and time to achieve ventilator weaning, will be presented.

6.5.1 Tidal Volume

Figure 6.4 shows example signals recorded using the spirometer and the respiratory effort belt positioned around the abdomen during a quiet breath, both with and without AFES. As can be seen in Figure 6.4(b), a stimulation artefact can be observed in the respiratory effort belt signal at the onset of stimulation. However, this stimulation artefact is only present for approximately the first 0.5 seconds of stimulation, after which the respiratory effort belt signal matches the spirometer signal. The short duration of this stimulation artefact means that it does not affect the respiratory effort belt signal during either the preceding, or proceeding, inhalation.

The stimulated and unstimulated V_T recorded from Participant 1 at each of the nine assessment sessions is shown in Figure 6.5. The stimulated and unstimulated V_T of the other eight participants who completed the study are shown in Appendix B.

Participant 1's stimulated V_T was found to be statistically significantly greater than unstimulated V_T at five of the nine (55.6%) assessment sessions. Their stimulated and unstimulated V_T was found to statistically significantly increase during three (37.5%) of the eight weeks of participation, with a statistically significant decrease observed during one of the eight (12.5%) weeks.

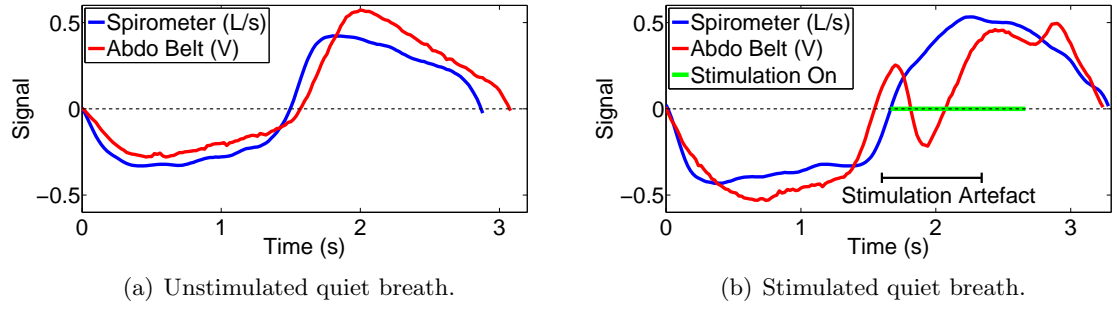


Figure 6.4: Signals recorded during quiet breaths taken by Participant 8 at assessment session A7, using a spirometer, shown in blue, and a respiratory effort belt positioned around the abdomen, shown in red. Figure 6.4(a) shows a quiet breath where stimulation is not applied. Figure 6.4(b) shows a quiet breath where stimulation is applied for one second at the onset of exhalation, shown in green. A stimulation artefact, which can be detected in the respiratory effort belt signal at the onset of stimulation, is also highlighted.

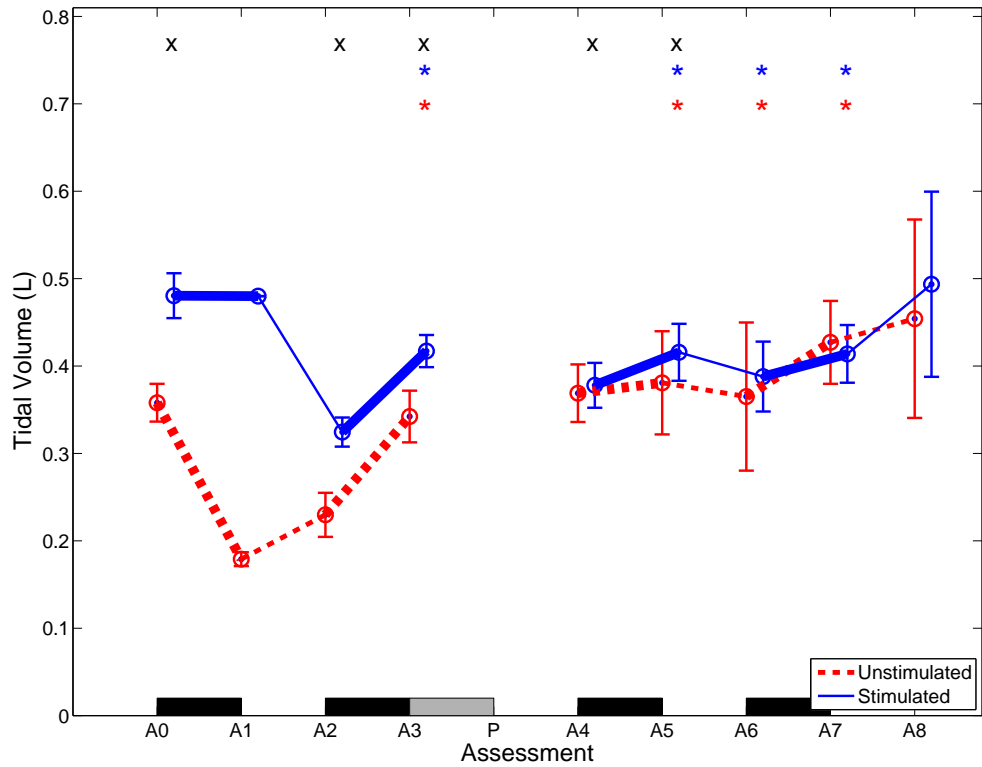


Figure 6.5: Tidal Volume (V_T) \pm standard deviation of Participant 1, recorded at nine weekly assessment sessions, where a blue line represents stimulated, and a red line unstimulated, breaths. Solid black line along the bottom of plot represents one week of AFES training, solid grey line along bottom of the plot represents one week of no training, due to patient developing pneumonia (P), and no line indicates week with no training. Black x indicates stimulated V_T was statistically significantly different to unstimulated V_T , blue * indicates that stimulated V_T was statistically significantly different to stimulated V_T recorded at previous assessment and red * indicates that unstimulated V_T was statistically significantly different to unstimulated V_T recorded at previous assessment.

Across all participants stimulated V_T was found to be statistically significantly greater than unstimulated V_T at 42 of the 80 (52.5%) assessment sessions and statistically significantly smaller at three of the 80 (3.8%) assessment sessions. Stimulated V_T was found to statistically significantly increase during 20 of the 71 (28.2%) combined weeks of participation and statistically significantly decrease between 12 (16.9%) of the weeks of participation. Fourteen (70.0%) of the increases occurred during weeks where AFES was applied, while three (25.0%) of the decreases occurred during weeks when AFES was applied. Unstimulated V_T was found to statistically significantly increase during 21 of the 71 (29.6%) combined weeks of participation and statistically significantly decrease during 12 (16.9%) of the weeks of participation. Of these increases 14 (66.7%) occurred during weeks where AFES was applied, while four (33.3%) of the decreases occurred during weeks when AFES was applied.

The mean V_T/kg of all nine participants at each of the nine assessment sessions is shown in Figure 6.6. There was no statistically significant difference between stimulated and unstimulated V_T/kg at any assessment session, or stimulated or unstimulated V_T/kg over the study duration. Stimulated V_T/kg increased in all weeks where AFES training was applied, but only increased in the final week when AFES training was not applied. The change in unstimulated V_T/kg was found to be similar during weeks with and without stimulation.

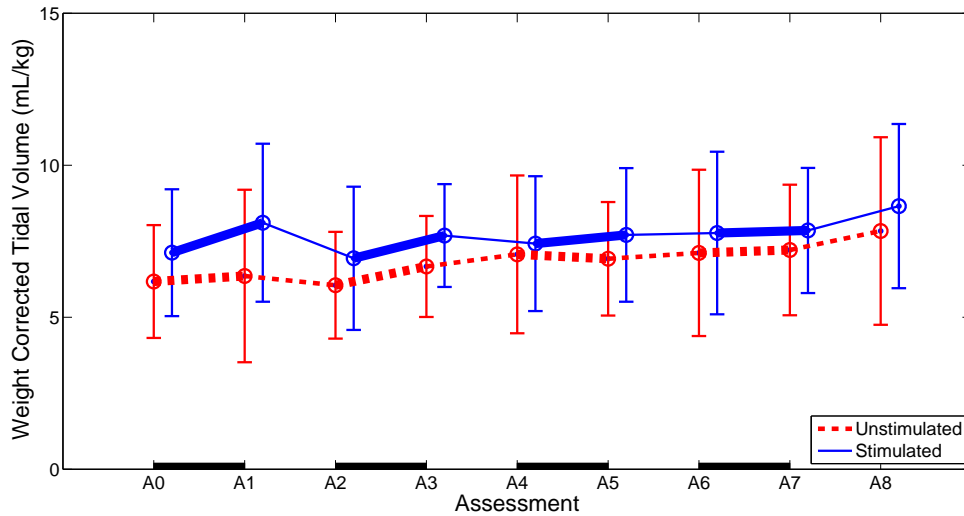


Figure 6.6: Mean weight corrected tidal volume (V_T/kg) \pm standard deviation for all nine participants, recorded at nine weekly assessment sessions, where a blue line represents stimulated, and a red line unstimulated, breaths. Solid black lines along the bottom of plot represent one week of AFES training and no line indicates one week with no training.

Figure 6.7 shows each participant's unstimulated V_T/kg at each of the nine assessment sessions. Participant 7 had the lowest unstimulated V_T/kg , with a mean of around 3 mL/kg across the study duration. Participant 7 was the only participant who received AFES training and did not wean from mechanical ventilation within the eight week study duration.

The group cumulative change in stimulated and unstimulated V_T/kg during weeks with and

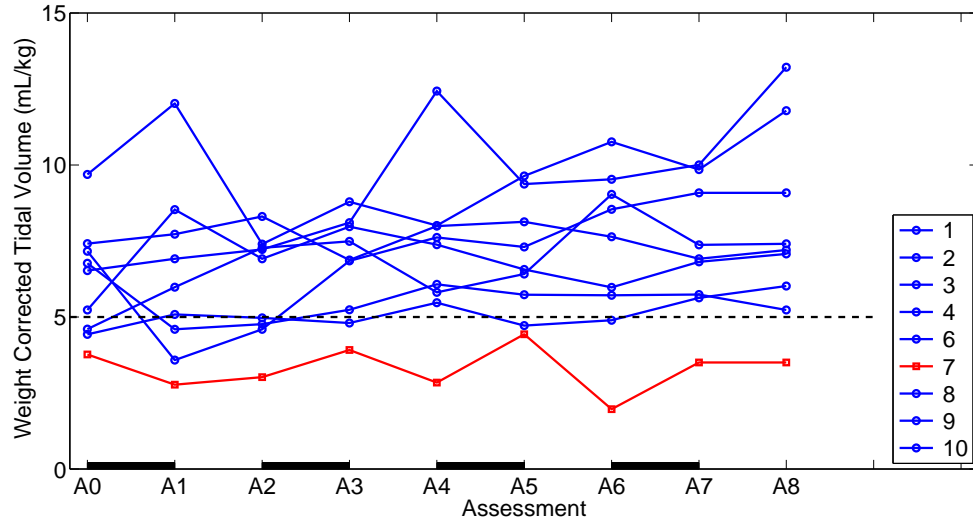


Figure 6.7: Unstimulated weight corrected tidal volume (V_T/kg) of all participants, recorded at nine weekly assessment sessions. Participant 7 is represented by a red line. A V_T/kg of 5 mL/kg is also marked, which is the point at which participants were expected to wean from mechanical ventilation.

without AFES training is shown in Figure 6.8. It can be seen that stimulated V_T/kg decreased in weeks without training over the study duration, while changes in unstimulated V_T/kg are similar throughout the study.

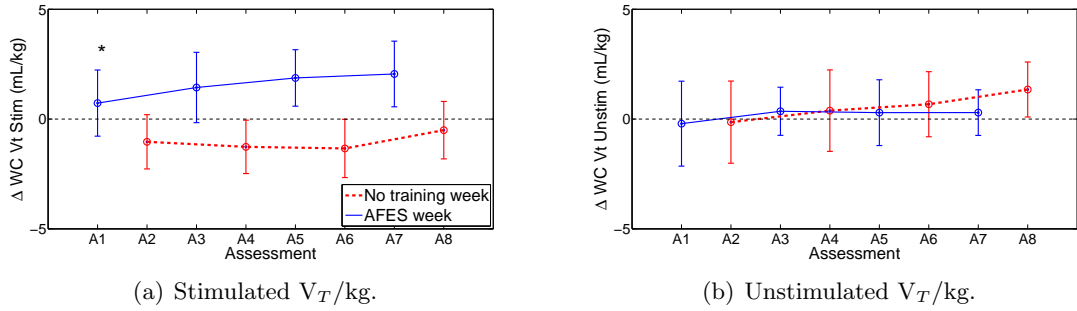


Figure 6.8: Group cumulative change in stimulated and unstimulated Weight Corrected (WC) Tidal Volume (V_T/kg) \pm standard deviation for all nine participants, recorded at nine weekly assessment sessions, where a blue line represents weeks with AFES training and a red line represents weeks without AFES training. Black * indicates change recorded after a week with AFES training was statistically significantly different to change recorded after the following week with no AFES training.

6.5.2 Vital Capacity

Stimulated and unstimulated V_C recorded from Participant 1 at each of the nine assessment sessions is shown in Figure 6.9. Also shown is the daily time spent breathing without ventilator support. The stimulated and unstimulated V_C of the other eight participants who completed the study, along with the daily time spent breathing without ventilator support,

are shown in Appendix B.

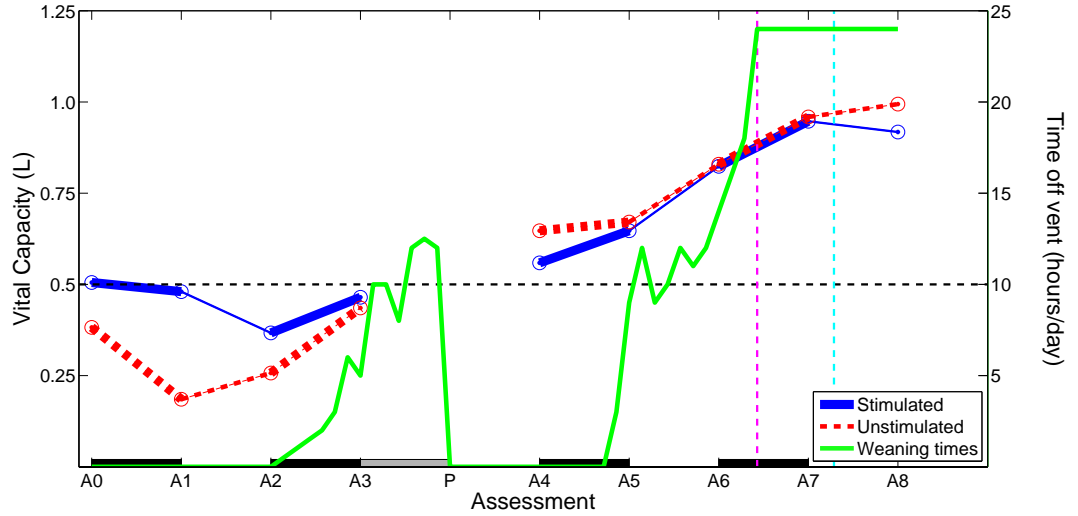


Figure 6.9: Vital Capacity (V_C) of Participant 1, recorded at nine weekly assessment sessions, where a blue line represents stimulated, and a red line unstimulated, breaths. Solid black line along the bottom of plot represents one week of AFES training, the solid grey line along the bottom of the plot represents one week of no training, due to patient developing pneumonia (P), and no line indicates one week with no training. Green line represents time spent breathing without ventilator support per day, while broken black line represent a V_C of 500 mL, the V_C at which participants were expected to wean based on clinical experience. The dashed magenta line represents the time point at which the participant achieved 24 hours of ventilator free breathing, while the dashed cyan line represents the time point at which the participant achieved seven days of ventilator free breathing.

Participant 1's V_C appeared to show a strong positive correlation to time spent breathing without ventilator support. It can also be observed that while the development of pneumonia in week four of the study delayed weaning, it did not appear to affect V_C , which increased slightly during the two weeks where Participant 1 received no AFES training.

Across all participants stimulated V_C was found to be clinically significantly greater than unstimulated V_C at nine of the 80 (11.3%) assessment sessions and clinically significantly smaller at two of the 80 (2.5%) assessment sessions. Stimulated V_C was found to increase clinically significantly during 17 of the 71 (23.9%) combined weeks of participation and decrease clinically significantly between 11 (15.5%) of the weeks of participation. Of these increases, 10 (58.8%) occurred during weeks where AFES was applied, while seven (63.6%) of the decreases occurred during weeks when AFES was applied. Unstimulated V_C was found to increase clinically significantly during 15 (21.1%) of the 71 combined weeks of participation and decrease clinically significantly between three (4.2%) of the weeks of participation. Of these increases, nine (60.0%) occurred during weeks where AFES was applied, while three (100%) of the decreases occurred during weeks when AFES was applied.

The combined mean of each participant's V_C /kg at each of the nine assessment sessions is

shown in Figure 6.10. For the combined data there was no statistically significant difference between either the stimulated and unstimulated V_C/kg during any assessment session, or the stimulated or unstimulated V_C/kg recorded over the study duration. Both stimulated and unstimulated V_C/kg increased throughout the study duration.

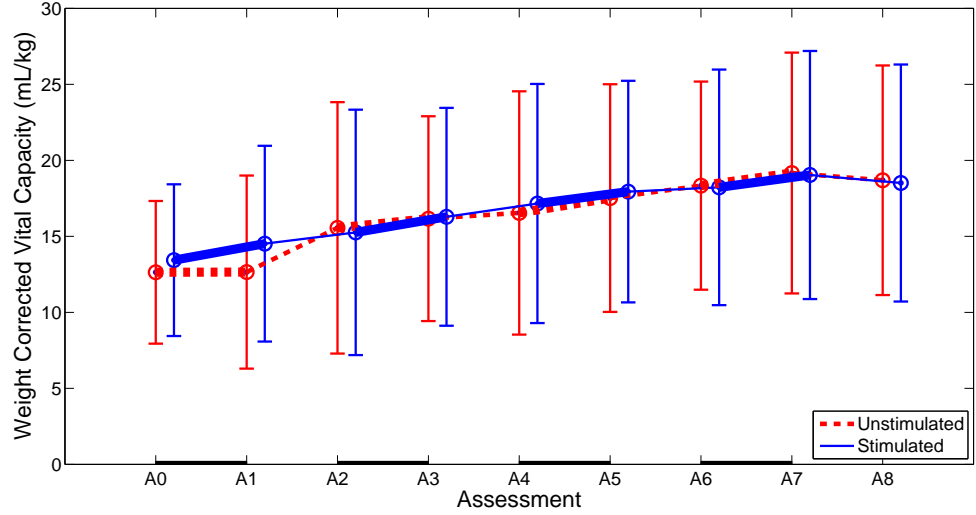


Figure 6.10: Mean weight corrected vital capacity (V_C/kg) \pm standard deviation for all nine participants, recorded at nine weekly assessment sessions, where a blue line represents stimulated, and a red line unstimulated, breaths. Solid black lines along the bottom of the plot represent one week of AFES training and no line indicates one week with no training.

The group cumulative change in stimulated and unstimulated V_C/kg during weeks with and without AFES training is shown in Figure 6.11. Stimulated V_C/kg increased to a greater degree during weeks of AFES training than without, while the changes in unstimulated V_C/kg are similar throughout the study.

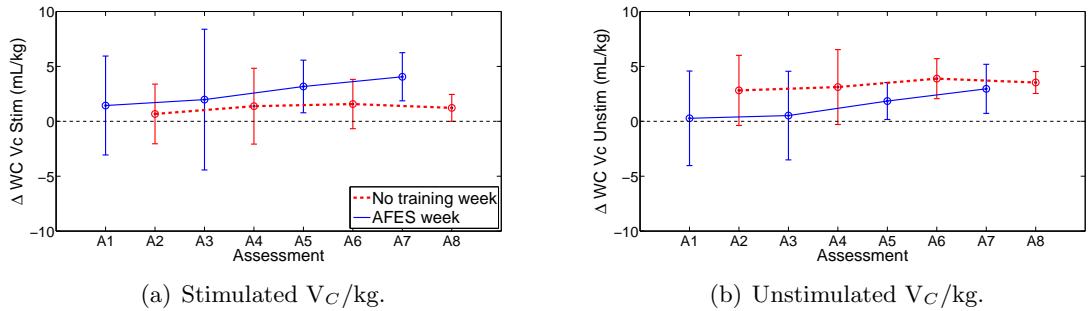


Figure 6.11: Group cumulative change in stimulated and unstimulated Weight Corrected (WC) Vital Capacity (V_C/kg) \pm standard deviation for all nine participants, recorded at nine weekly assessment sessions, where a blue line represents weeks with AFES training and a red line represents weeks without AFES training.

6.5.3 Time to Wean

Participant 7, and the control participant matched to Participant 6, did not wean from mechanical ventilation during the study. All other participants went through a standard weaning procedure whereby after reaching short term (24 hours) weaned no further mechanical ventilation was necessary. Figure 6.12(a) and Figure 6.12(b) show the group time to achieve short term and long term weaning respectively, while Table 6.4 shows the time to wean for each participant from the date of initial ventilation, with the group mean also shown. From Table 6.4 it can be seen that five of the nine (55.6%) participants who received AFES training weaned from mechanical ventilation at a faster rate than their matched control participant. The intervention participants weaned from mechanical ventilation on average 11 days faster than the control participants. However, the group means were not found to be statistically significantly different. It should be noted that the grouped data presented in Table 6.4 and Figure 6.12 ignore the data for a participant in each group who did not wean from ventilation.

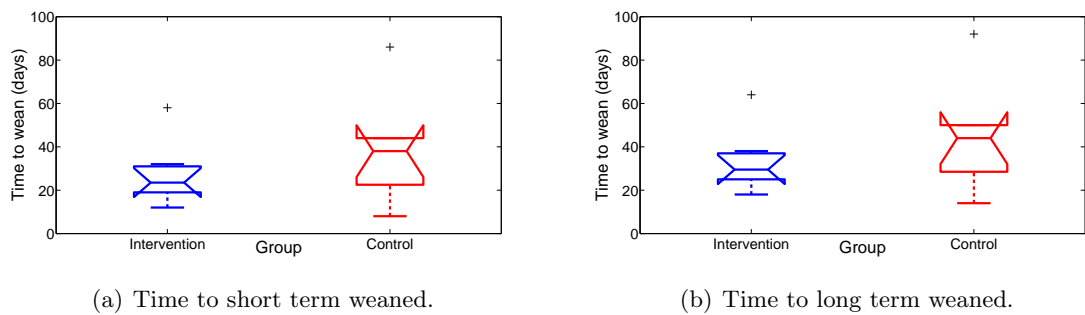


Figure 6.12: Boxplots showing time to wean for the Intervention (blue) and Control (red) groups. Each box shows the median together with the inter-quartile range, with outliers marked by a black +. a) shows the time to achieve 24 hours of ventilator free breathing, denoted short term weaned. b) shows the time to achieve seven days of ventilator free breathing, denoted long term weaned.

Table 6.4: Time to wean for each participant who received AFES training from date of initial ventilation. Also shown is the time to wean for their matched control. Short term weaned is a period of 24 hours without ventilation and long term weaned is a period of seven days without ventilation. Participants who did not wean from ventilation are denoted by N/A. The means of each group \pm standard deviation (s.d.) are also shown, which do not include the data of Participant 7 and control Participant 6 due to these participants not weaning from ventilation.

ID	AFES		Control	
	Short Term Weaned (days)	Long Term Weaned (days)	Short Term Weaned (days)	Long Term Weaned (days)
1	58	64	42	48
2	22	28	33	39
3	12	18	34	40
4	32	38	86	92
6	30	36	N/A	N/A
7	N/A	N/A	45	51
8	25	31	8	14
9	21	27	12	18
10	17	23	44	50
Mean \pm s.d.	27 \pm 14	33 \pm 14	38 \pm 24	44 \pm 24

6.6 Discussion

The primary aim of this study was to evaluate the feasibility of using AFES to assist acute ventilator dependent tetraplegics in weaning from mechanical ventilation. The feasibility of this intervention has been demonstrated here for the first time, by applying AFES in a clinical setting with nine participants during four weeks, over an eight week period, without any negative side effects and a high compliance of the participants to the training sessions (see Section 6.6.2). The effectiveness of the intervention was demonstrated by the increases in respiratory function that were observed throughout the study duration.

6.6.1 Improvements in Respiratory Function

Acute Effect The stimulated V_T of each participant was statistically significantly greater than unstimulated V_T at 55.6 percent of the assessment sessions. While this agrees with previous studies which also found an acute increase in V_T during the application of AFES [120, 121], the extent of this increase differs across studies. Sorli *et al.* [120] applied AFES to the rectus abdominis muscles during quiet breathing with nine able bodied participants. They found that the V_T of the able bodied participants increased by 65% during AFES. This increase is much greater than the average increase of approximately 15 percent observed here. However, Sorli *et al.* do not report the stimulation intensity used to achieve this increase. It may be that a much larger stimulation intensity was used than with the participants in this study. As some of the participants in this study retained sensation of the

abdomen, stimulation intensity was set at a level that achieved a visible muscle contraction. It may be that a higher level of stimulation intensity would have achieved a greater increase in V_T . Stanic *et al.* [121] reported an increased in V_T of 35 percent with the chronic tetraplegic population, and 34 percent with the able bodied population, using a similar stimulation intensity as was used in this study. While this is still a greater increase than observed here, all three studies used different electrode locations to apply AFES. The difficulty in comparing AFES studies caused by a lack of common clinical protocol is discussed in further detail in Section 8.2. Finally, the participants in this study were ventilator dependent and were likely to be suffering from muscle weakness associated with critical illness [125]. This may be another contributing factor as to why the acute increase in V_T during AFES observed here was less than that observed with the able bodied and chronic tetraplegic population.

Stimulated V_C was only clinically significantly greater (more than 200 mL) than unstimulated V_C at 11.3 percent of the assessment sessions. It may be that a value of 200 mL, which represented a greater than 20 percent acute increase in V_C for some participants, is too large for this population and requires to be revised for future studies.

Longitudinal Effect Stimulated and unstimulated V_T/kg and V_C/kg increased throughout the study. This agrees with previous studies that also showed an increase in V_C after AFES training [70, 73, 124]. However, neither of these changes were found to be statistically significant. V_T/kg was not expected to greatly increase as once a participant reaches a V_T at which they are able to breathe comfortably there is no need for further increase. The lack of a statistically significant increase in V_C/kg is largely due to the large standard deviation of the data. A larger study may reduce this deviation, leading to a greater likelihood of achieving a statistically significant increase in V_C/kg after AFES training.

With any intervention study in the acute spinal cord injured population it is difficult to distinguish between the effect of an intervention and ‘natural recovery’. By applying AFES on alternate weeks it was hoped that it would be possible to identify improvements in respiratory function caused by the intervention. It was found that stimulated and unstimulated V_T increased statistically significantly during 28 and 30 percent of weeks respectively. Of these increases, 70.0 and 66.7 percent occurred during weeks where AFES was applied, indicating that a statistically significant increase in V_T is more likely to be observed after a week of AFES training. Stimulated and unstimulated V_C increased clinically significantly during 24 and 21 percent of weeks respectively. Of these increases, 58.8 and 60.0 percent occurred during weeks where AFES training was applied, again indicating a greater likelihood of achieving a clinically significant increase in V_C during a week where AFES training was applied. These results indicate that there may be an effect from AFES training, although further work is required to quantify this effect.

Liaw *et al.* [113] found a statistically significant 27 percent increase in Forced Vital Capacity

(FVC) over a six week period for sub-acute tetraplegics who received no intervention. In this eight week intervention study it was found that unstimulated V_C /kg increased by 48 percent. This is greater than the increase observed by Liaw *et al.* and suggests that there may be an intervention effect from AFES training. Rather than natural recovery, the increases in respiratory function observed during non treatment weeks may be caused by an acute carry over effect from the previous week's AFES training. Although there is no literature investigating the duration, or presence, of the carry over effect from AFES, previous studies have found a carry over effect from FES training of the lower limbs to correct foot drop [57, 167]. However, the duration of such a carry over effect has not been established and is disputed in the literature. There are two possible approaches to determine whether there is a carry over effect from AFES training. The first approach would be to randomise the order of treatment, *i.e.* AFES training may commence in either week one or week two of the study, which will give an indication as to whether respiratory function increases in the first week of the study when no AFES training is applied. A second approach would be to increase the duration of the control periods. By having a one week treatment period and a two week control period any acute carry over effect of the AFES training should have diminished to a greater extent than in this study. The drawback of this approach is an increased study duration and a reduction in AFES application in the early stages when it is thought to be most beneficial. The majority of participants in this study weaned from mechanical ventilation in the first few weeks. An increased control duration would reduce the amount of AFES training that each participant received while dependant on mechanical ventilation. This may reduce the benefit of the intervention for this patient group.

Ventilator Weaning It was found that five of the nine (55.6%) participants who completed the intervention weaned from mechanical ventilation at a faster rate than their matched controls, with one participant in each group not weaning from mechanical ventilation. When these two participants were ignored it was found that participants who received AFES training weaned from mechanical ventilation on average 11 days faster than their matched controls. While the numbers in this study are too small for this difference to be statistically significant, this finding indicates that the application of an AFES training program may enable faster weaning from mechanical ventilation.

Clinically, a value of 500 mL is often used as the V_T at which people are predicted to wean from mechanical ventilation. However, this does not take into account a persons body weight, with a greater body weight inherently leading to an increased V_T and V_C . This was highlighted by Participant 1, whose weight was 50 kg, weaning from ventilation despite their V_T being less than 500 mL for the whole study duration, while Participant 7, whose weight was 82 kg, did not wean from ventilation despite achieving similar V_T values. In this study all of the participants, except Participant 7 who did not wean from ventilation, achieved a V_T /kg of greater than 5 mL/kg, suggesting this may be an indicator for weaning success in the tetraplegic population.

6.6.2 Other Observations

For electrical stimulation to be successful the LMNs, which carry motor information from the spinal cord to a muscle, must be intact (See Section 1.3 for further information). It was later established that Participant 5, who was a non responder to stimulation, had suffered LMN damage, either at the time of SCI or due to a large edema (extra cellular fluid [168]) which was later observed in the spinal cord. This participant was discharged from hospital requiring full time ventilatory support. The impact of LMN damage on electrical stimulation is discussed in further detail in Section 8.4.

Participant 7 did not wean from ventilation during the study, which may be attributed to this participant's poor health after injury. Additionally this participant, along with the chronic participant who took part in the case study described at the start of this chapter, had a large amount of edema in the abdomen. This resulted in these participants requiring a much larger amount of stimulation current to initiate a contraction of the abdominal muscles (see Table 6.3 and Section 6.2.1), which may pose a problem for participants who retain sensation of the abdomen. The impact of edema on the effectiveness of AFES is discussed in further detail in Section 8.4. Interestingly Participant 7 had a cardiac pacemaker, with no negative effects of stimulation observed. This agrees with the findings of Shade [169]. Despite these problems the finding that two out of 10, or 20 percent, of the acute participants did not wean from mechanical ventilation agrees with the findings of Gay [81], who states that every year in the USA 2700 acute tetraplegics require ventilation in the acute stage of injury but ultimately wean, while 500 (18.5%) require permanent mechanical ventilation. These results are similar to those reported by Martin *et al.* [87] who applied inspiratory muscle training, using a pressure threshold device, to assist weaning from mechanical ventilation for 10 able bodied participants. They found that nine out of the 10 (90%) participants weaned from mechanical ventilation within a six week intervention protocol.

Participant 1 developed pneumonia during week four of the study and was unable to participate in AFES training for one week. During this time the participant returned to being ventilator dependant, with SBTs resuming after the pneumonia had cleared. For this participant the study duration was extended to take account of the missed week. Of the eight participants who weaned, Participant 1 had the lowest absolute value of V_T (although not the lowest V_T/kg) for the first three assessment sessions. They also took the longest time to wean from mechanical ventilation and were the only participant to suffer from a respiratory complication during the study. This suggests that a low V_T may be an indicator of increased weaning time and increased susceptibility to respiratory complications. The impact of AFES on respiratory complications is discussed in further detail in Section 8.2.2.

The development of this respiratory complication highlights the challenges of attaining a high compliance in a study with the acute tetraplegic population. However, except for this

week of pneumonia for Participant 1, and Participant 7 missing the final assessment session due to poor health, all other training sessions were met. This represented a compliance rate of 96.7 percent. McBain *et al.* [73] report a similar compliance rate of 97.8 percent when conducting AFES training with the chronic tetraplegic population. While McLachlan *et al.* [70] present no compliance rate, they indicate that one of the chronic patients missed an assessment session due to ‘personal time constraints’. Such problems are inherent with conducting studies with the chronic tetraplegic population. However, in this study all patients were less independent and were heavily reliant on caregiver support. For this reason AFES training could be incorporated as part of their normal daily rehabilitation program, making missed sessions for any other reason than poor health unlikely.

Another interesting observation was that AFES training sessions tended to lead to an increased demand for removal of secretion from the airways, both during the training sessions and for a short period after. Although this outcome could not be quantified and the evidence was largely anecdotal, it was observed by the researchers, clinicians and participants. This observation is not entirely surprising as AFES causes the abdomen to move in a similar motion as during a manually assisted cough (see Section 2.3.2.1). The use of AFES to aid secretion removal, and hence improve respiratory health, may improve the effectiveness of mechanical insufflation-exsufflation. This possibility was further investigated in Chapter 7.

Lee *et al.* [122] used AFES to assist ventilator weaning and tracheostomy decannulation for one chronic C4 tetraplegic patient. The results observed here when using AFES with the acute tetraplegic population, and with a chronic tetraplegic participant in the case study reported at the start of this chapter, suggest that for ventilator dependant tetraplegics who retain some diaphragm function (*i.e.* an injury level of C3 and below) the principles described here may be used to increase respiratory function and aid faster weaning from mechanical ventilation. This would in turn lead to a significant improvement in this patient groups quality of life, reduce susceptibility to respiratory complications and result in a cost saving for the local health care provider.

6.6.3 Limitations

A number of limitations of this study were identified. Firstly, from a clinical viewpoint, a continuous training protocol may be more beneficial for patients than the week on week off protocol adopted here, as patients would receive a higher dose of the intervention. However, this protocol was used to highlight the effectiveness of AFES, which should aid its clinical introduction. As a result of this study, a continuous training protocol will shortly be introduced at the QENSIU to assist all acute ventilator dependent tetraplegic participants in weaning from mechanical ventilation. Additionally, many of the participants in this study had a V_C of less than 1 L. The ATS/ERS standards for spirometry [129] suggest that for a person with a V_C of less than 1 L, their V_C should be the maximum breath that is within 0.1 L of another. Although the ATS/ERS standards have been shown to be applicable

for chronic (in this case greater than one year post injury) tetraplegic participants [130], a repeatability value of 0.15 L was used for all participants in this study to allow for the large variations in values that were observed when McLachlan *et al.* [70] performed a V_C test with the sub-acute and chronic tetraplegic population. Participant 6 suffered a stroke that is thought to have occurred during week two or three of their participation in this study. This stroke left the participant with a slightly impaired ability to follow instructions, making the recording of accurate V_C results more difficult. However, with encouragement from the participants regular caregiver, it was possible to record a V_C measurement that was believed to be accurate as it met the ATS/ERS standards.

This study aimed to recruit participants as soon as possible after ventilation. While Participant 10 started the study two days after ventilation commenced, they were the only participant recruited in the first five days after ventilation. Many of the participants in this study spent time on a high dependency ward outside the QENSIU before being admitted to the QENSIU for specialist SCI care. In the cases of Participant 2 and Participant 4 this initial care was provided outside of the United Kingdom, resulting in these participants being recruited slightly after the four week acute injury period. Participant 7 was recruited for this study 22 days post injury. However, due to repeated poor health this participant did not actually commence on the study until 43 days post injury. Due to the apparent reduction in time spent dependent on mechanical ventilation after an AFES training program, earlier recruitment may lead to a greater benefit from the intervention.

A previous study by Girard *et al.* [166] suggests a SaPO_2 of 88 percent as the point at which heterogeneous participants in an intensive care unit should be reconnected to mechanical ventilation during SBTs. However, in line with current clinical procedures at the QENSIU, a SaPO_2 of 92 percent was deemed the appropriate level at which participants should be reconnected to mechanical ventilation during this study. Using SaPO_2 of 88 percent as the point at which participants were reconnected to mechanical ventilation would have increased the time that participants spent breathing independently, which may have led to a greater improvement in respiratory function.

Finally, many of the participants had their tracheostomy removed during the study, which often left a large stoma. Although this stoma quickly healed, its presence could make assessment sessions difficult. The removal of Participant 6's tracheostomy, during week seven of the study, left a large stoma from which there was a large amount of air leakage during assessment session seven (A7). This assessment was repeated the following day after the stoma had been sealed by a trained clinician, which greatly reduced the air leakage and led to a 200 mL increase in the measured V_T . The stoma had healed significantly by assessment session eight (A8), during which there was not deemed to be any air leakage. Participant 1 had their tracheostomy cuff removed during week eight of the study. At assessment session eight (A8) the tracheostomy was capped and the respiratory flow was measured using a spirometer

coupled with a full face mask. However, with the participant in the supine position there was a large amount of air leakage under the mask. This assessment session was repeated the following day with the spirometer coupled with a mouthpiece rather than a face mask. This method proved to be more effective and was adopted to measure the respiratory flow of all participants who no longer had a cuffed tracheostomy.

6.7 Conclusion

The results of this study indicate that AFES is a feasible technique for assisting ventilator weaning for people with acute tetraplegia. AFES training was also shown to improve the respiratory function of this population, with an associated decrease in the time spent dependant on mechanical ventilation observed.

Chapter 7

Abdominal FES to Improve Respiratory Function in Sub-acute Tetraplegia

“The scientific man does not aim at an immediate result. He does not expect that his advanced ideas will be readily taken up. His work is like that of the planter - for the future. His duty is to lay the foundation for those who are to come, and point the way. He lives and labors and hopes.”

Nikola Tesla

7.1 Summary

Previous research has shown that an Abdominal Functional Electrical Stimulation (AFES) training program can improve the respiratory function of people with tetraplegia. The optimal training protocols, in particular the training duration that achieves the greatest improvement in respiratory function, have yet to be established. Additionally, findings outlined in the previous chapter indicate that AFES may cause increased loosening of lung secretions. In this chapter, a randomised crossover study is presented that investigates the feasibility of applying an extended AFES training program with the sub-acute tetraplegic population. Three non ventilator dependent tetraplegic patients participated in pilot experiments outlined in this chapter. Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF) and Forced Exhaled Volume in one second (FEV_1) were measured fortnightly, with and without AFES. The feasibility of combining AFES with Mechanical Insufflation-Exsufflation (MI-E) was assessed with one tetraplegic participant by measuring respiratory function during MI-E, again with and without AFES. The application of AFES led to an acute increase in FVC, PEF and FEV_1 . FVC, PEF and FEV_1 increased throughout the study, with FVC increasing at a greater rate during the AFES training period than during the control period. Combining AFES with MI-E led to an acute increase in respiratory function at the majority of assessment sessions. While the feasibility of these two novel protocols was demonstrated, additional participants are required to fully assess the effectiveness of these interventions and establish the optimum AFES training duration.

7.2 Background

Respiratory complications are a leading cause of morbidity and mortality for the tetraplegic population [29]. People with tetraplegia have poor respiratory function and are unable to generate an effective cough (see Section 1.4.3). Therefore, these respiratory complications are primarily attributed to respiratory infections caused by the build up of secretions in the lungs and airways. Previous work within our group [70] indicated that a three week AFES training program led to a statistically significant increase in the FVC of 12 participants with sub-acute and chronic tetraplegia. This increase in FVC was associated with improved cough generation, which should reduce the likelihood of respiratory infection. The results of this study showed that FVC had not plateaued by the end of the three week intervention period, indicating that a longer training period may lead to further improvements in respiratory function.

Clinically, the problem of secretion removal for the tetraplegic population is often addressed by using tracheal suctioning, where suction is applied via a patients tracheostomy tube to remove secretions. While tracheal suctioning can be used to successfully remove secretions, it is uncomfortable for the patient, often misses the left bronchus and does not directly loosen secretions. To aid the loosening of secretions assisted coughing, which is designed to

simulate a cough, is often employed. Assisted coughing is usually delivered in one of two ways, namely a manually assisted cough or Mechanical Insufflation-Exsufflation (MI-E). A manually assisted cough involves a caregiver applying pressure to the thoracoabdominal cavity during the exhalation phase of a voluntary cough. The requirement for a care giver to apply this approach has cost and resource implications for the local health care provider [91, 92]. The force used by the caregiver to generate an effective cough is subjective, leading to a variability in the success of this approach. MI-E applies alternating positive and negative pressure to the user's airway to simulate a cough and loosen secretions, with suction applied after each simulated cough to remove these secretions. This mechanical system provides a cheaper and easier to implement alternative to manually assisted coughing. During the study presented in Chapter 6 it was observed that AFES led to an increased need for secretion removal, indicating that AFES was loosening lung secretions. The combination of AFES with MI-E, hypothesised to lead to an additional improvement in cough generation and secretion clearance compared to MI-E alone, is investigated here.

The aims of this study were i) to evaluate the feasibility and effectiveness of an extended AFES training program to improve the respiratory function of sub-acute tetraplegic participants and ii) to evaluate the feasibility of combining AFES with MI-E.

7.3 Methods

Four tetraplegic inpatients at the Queen Elizabeth National Spinal Injuries Unit (QENSIU) were recruited for this study, with the participant demographics shown in Table 7.1. Ethical approval was granted by the National Health Service West of Scotland Research Ethics Committee (Local Code: 13/WS/0002). All procedures conformed to the Declaration of Helsinki and all participants gave written informed consent. It should be noted that the sub-acute phase of injury begins approximately four weeks after injury (see Section 1.2.3.2), with three of the participants recruited for this study before this point. However, due to half of the participants undergoing a four week control period before any intervention is applied, coupled with the eight week duration of the intervention period (meaning participants will only receive a small dose of the intervention in the acute period of injury), all patients in this study will be regarded as sub-acute.

Participants were recruited according to the following inclusion and exclusion criteria.

Inclusion criteria:

1. Men or women over 16 years of age;
2. Reduced respiratory function as a result of tetraplegia;
3. No reliance on mechanical ventilation;
4. Good visual response to surface electrical stimulation of the abdominal muscles, suggesting that lower motor neurons are intact.

Exclusion criteria:

1. Under 16 years of age;

Table 7.1: Participant demographics showing sex, age, injury level, American Spinal Injuries Association Impairment Scale (AIS) level (see Section 1.2.3.2), weight and time post injury at recruitment.

Participant	Sex	Age (years)	Injury level	AIS level	Weight (kg)	Time post injury (days)
1	M	69	C6	A	74	26
2	M	19	C6	A	80	22
3	M	24	C5/6	C	83	19
4	M	20	C5	C	69	29

2. Female participants who are pregnant;
3. Significant history of autonomic dysreflexia;
4. No visual response to surface electrical stimulation of the abdominal muscles, suggesting that lower motor neurons are not intact;
5. Unstable chest or abdominal injury;
6. Bulbar dysfunction;
7. Participant unable to give informed consent.

As with the clinical study outlined in Chapter 6, participants were recruited by consultants at the QENSIU, based on the inclusion and exclusion criteria outlined above. However, the ultimate decision for inclusion was based on the clinical judgement of the consultant.

7.3.1 Experimental Procedures

The study took the form of a randomised crossover design, consisting of a four week control period and an eight week training period, with this training period followed by a two week follow up/wash out period, resulting in a total duration of participation of 14 weeks. The order of the control and training periods was randomised for each participant. At a pre-study assessment, and at the end of every second week, an assessment session was conducted. An effort was made to perform all procedures at the same time of day and all procedures were performed at the participant's bedside with the participant in a supine position. The study timeline is shown in Figure 7.1 and described in further detail below.

7.3.1.1 Pre-study Assessment

After recruitment each participant took part in a pre-study assessment, which also served as a familiarisation session. At this session AFES was applied to the rectus abdominis and external oblique muscles to ascertain whether these muscles responded to electrical stimulation. If a contraction was achieved the optimum stimulation current and pulsewidth required to induce a visible contraction of these muscles was established. After the optimum stimulation parameters had been established, a full assessment session (see Section 7.3.1.4) was conducted

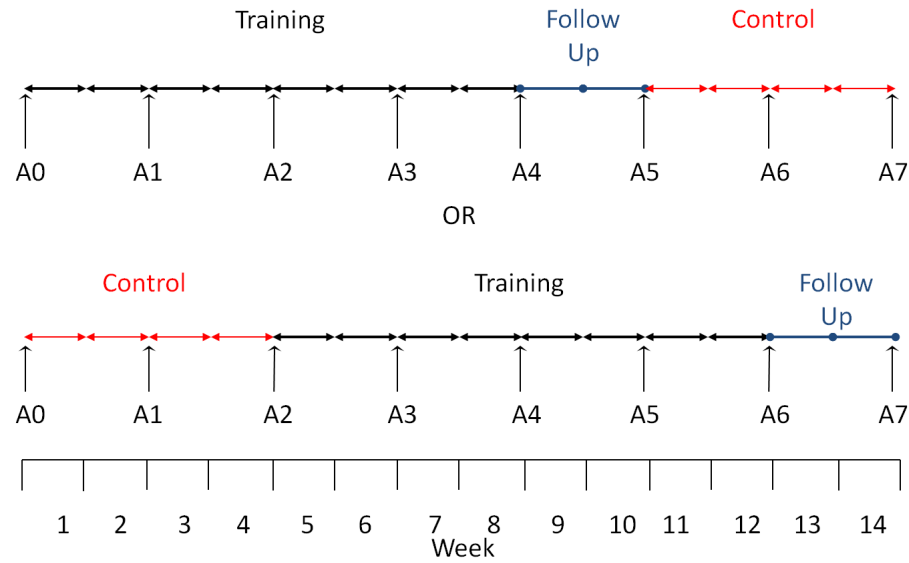


Figure 7.1: Study timeline indicating control (red), training (black) and follow up/wash out (blue) periods. Assessment sessions are also indicated.

(denoted on Figure 7.1 as A0).

7.3.1.2 Training Sessions

AFES training sessions were conducted five times per week (Monday to Friday) for a total of eight weeks. During each training session AFES was applied to the rectus abdominis and external oblique muscles for 40 minutes, using the stimulation current established at the pre-study assessment. Pulswidth was adjusted throughout each training session to account for muscle fatigue. The aim of these training sessions was to strengthen the abdominal muscles.

7.3.1.3 Follow up/Wash out Period

Each training period was followed by a two week follow up period. If the training period preceded the control period the follow up also served as a wash out period, used to minimise the impact of any carry over effect from the training to the control period. During this follow up period no AFES training was performed, but a scheduled assessment session was conducted at the end.

7.3.1.4 Assessment Sessions

Fortnightly assessment sessions were conducted throughout the 14 week study duration. At each assessment session a series of FVC manoeuvres were performed with and without AFES, with the success of each manoeuvre judged using the protocol described in Section 3.2. To conduct an FVC manoeuvre participants were instructed to inhale to maximum lung capacity and exhale as fully and as forcibly as possible, with verbal encouragement provided. This manoeuvre was repeated up to five times, both with and without stimulation, to form one run. A second run of FVC manoeuvres was performed after a rest period of approximately

two minutes, providing a total of up to 10 stimulated and unstimulated FVC attempts in each assessment session. Whether stimulation was applied during the first or second set of five FVC manoeuvres within each run was randomised for each participant at each session. FVC is the largest exhaled volume, of at least three successful FVC manoeuvres, which is within 0.15 L of another attempt. From the FVC manoeuvres FEV_1 and PEF were also calculated. FEV_1 is the largest volume recorded during the first second of an exhalation, of at least three successful FVC manoeuvres, which is within 0.15 L of another attempt. PEF is the largest exhaled flow rate, from at least three successful FVC manoeuvres, which is within 0.67 L/s of another attempt.

7.3.1.5 MI-E Sessions

Participant 1 also took part in fortnightly MI-E sessions (on alternate weeks to the assessment sessions outlined above), at which cycles of MI-E were applied both with and without AFES. Each MI-E cycle had an insufflation pressure of 20 cmH₂O and an exsufflation pressure of -20 cmH₂O. The exsufflation period was three seconds, the insufflation period two seconds, with a pause of two seconds between each cycle.

During each MI-E cycle the participant was asked to inhale as fully as possible during the insufflation phase and exhale as fully and as forcibly as possible during the exsufflation phase. This provided a measure of Exhaled Volume (EV). Following the protocol used by Goncalves *et al.* [95], and the standard clinical protocol at the QENSIU, five insufflation-exsufflation cycles were applied during both unassisted and AFES assisted MI-E, to form one run. This provided five stimulated and five unstimulated measures of EV. A second run of MI-E was then conducted after a rest period of approximately two minutes, providing a total of 10 stimulated and 10 unstimulated measures of EV at each assessment session. From these 10 breaths the participant's maximum EV and the Peak Flow (PF) measured during these exhalations were calculated. EV is the largest exhaled volume which is within 0.15 L of another attempt. PF is the largest exhaled flow rate which is within 0.67 L/s of another attempt. It should be noted that due to the short insufflation and exsufflation periods, FVC and PEF, which require the participant to inhale and exhale as fully as possible without any limitation put on the length of these periods, could not be recorded. Whether stimulation was applied during the first or second set of five MI-E cycles within each run was randomised at each session.

7.3.2 Equipment

During AFES training sessions the participant's respiratory activity was detected using a respiratory effort belt positioned around the abdomen. During assessment sessions respiratory activity was recorded using a spirometer, which was attached to a mouthpiece. These methods are described in further detail in Section 3.3. Data was collected and pre-processed using the

methods described in Section 3.3.

7.3.2.1 MI-E

MI-E was applied using a commercially available MI-E system (Cough-Assist, Phillips Respironics, Netherlands), via a mouthpiece, which was connected to the MI-E tubing as shown in Figure 7.2. A nasal clip was used to prevent air leakage at the nose, with participants instructed to form a seal at the mouth to prevent air leakage there. A pressure sensor was fitted in line with the MI-E tubing to detect the insufflation and exsufflation periods of the MI-E device. During the MI-E assessment sessions the participant's respiratory function was measured using a spirometer as described in Section 3.3. This spirometer was attached to a respiratory flow head, which was fitted in line with the MI-E tubing as shown in Figure 3.8.

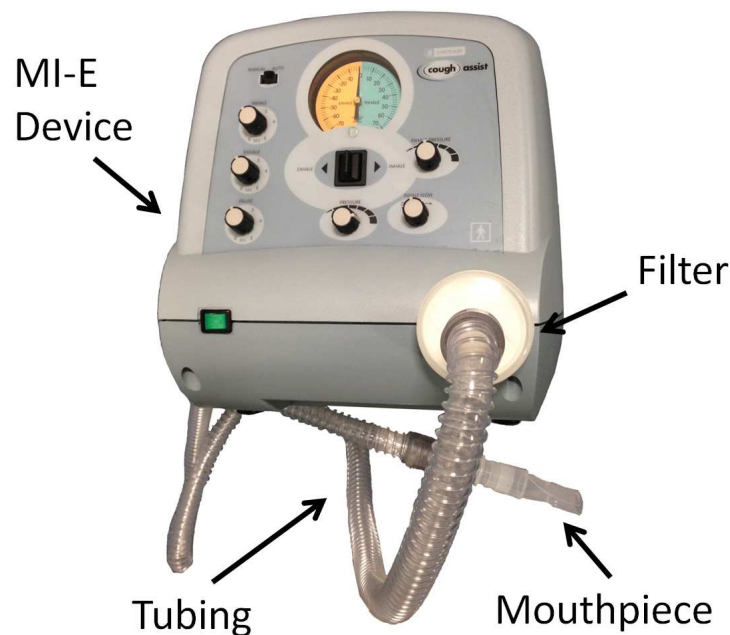


Figure 7.2: Mechanical Insufflation-Exsufflation (MI-E) system showing the MI-E device, the tubing connecting the device with the user, a filter used to prevent secretion entering the machine and the mouthpiece.

7.3.2.2 Stimulation System

The stimulation system described in Section 3.4.1 was used to apply AFES during this study. Stimulation was applied in synchrony with the participant's respiratory activity: i) during training sessions using the signal from a respiratory effort belt positioned around the abdomen ii) during assessment sessions using the signal from a spirometer, and iii) during MI-E sessions using the signal from the pressure sensor fitted in line with the MI-E tubing (automatic stimulation methods are explained in more detail in Section 3.4.3). Electrodes were positioned at the motor points of the rectus abdominis and external oblique muscles, located using the protocol outlined in Chapter 5. The stimulation current required to achieve a visible muscle contraction at the pre-study assessment (with a pulsewidth of $100 \mu s$) was used at all

subsequent sessions and is shown for each participant in Table 7.2. Stimulation pulsewidth was varied between 100 and 500 μs within each session to account for muscle fatigue.

Table 7.2: Stimulation currents applied to the External Oblique (EO) and Rectus Abdominis (RA) muscle groups to achieve a visible contraction for each participant at the pre-study assessment session. These stimulation currents were used at all subsequent sessions.

Participant	Right EO (mA)	Left EO (mA)	Right RA (mA)	Left RA (mA)
1	40	30	60	40
2	80	80	80	80
3	30	30	30	30
4	50	50	35	35

7.3.3 Analysis and Outcome Measures

The primary outcome measure in this study was respiratory function, which was quantified using FVC, PEF and FEV₁. Individual results recorded from each participant are presented as FVC, PEF and FEV₁, with FVC and FEV₁ measured in litres (L) and PEF measures in litres per second (L/s). Group results are normalised by weight and are presented as weight corrected FVC (FVC/kg), weight corrected PEF (PEF/kg) and weight corrected FEV₁ (FEV₁/kg).

Participant 2 withdrew from the study, and their results were not used for analysis. Each of the remaining three participants took part in eight assessment sessions, giving a total of 24 assessment sessions. Conducting fortnightly assessment sessions over the 14 week study duration provided seven longitudinal comparisons for each participant (*i.e.* A0 compared to A1), giving a total of 21 longitudinal comparisons. The longitudinal change in respiratory function over the total study duration, the eight week intervention period and the four week control period was assessed by calculating i) the absolute change over the period ii) the percentage change over the period, defined as the change over the period divided by the initial value, and iii) the absolute change normalised by the total number of weeks within each period.

The unstimulated FVC data recorded during the 24 assessment sessions was tested for normality using the Shapiro-Wilk test. Based on the results of this test a two-way analysis of variance (ANOVA) was used to test for longitudinal changes in FVC/kg, PEF/kg and FEV₁/kg. A one-way ANOVA was used to test for a statistically significant difference in the FVC/kg, PEF/kg and FEV₁/kg recorded at each assessment session. In the case of significance (p-value of less than 0.05), post hoc multiple comparisons were performed using the Tukey-Kramer honest significant difference test to identify statistically significantly

different pairs. As FVC is the maximum value recorded at an assessment session, it was not possible to test for a statistically significant difference between the stimulated and unstimulated FVC recorded at any individual assessment session, or for longitudinal changes in stimulated and unstimulated FVC, for each participant. On the advice of clinical colleagues, it was agreed that an increase in FVC of 200 mL was regarded as clinically significant.

For the participant who took part in the MI-E session their respiratory function was quantified using EV and PF, which were measured in L and L/s, respectively.

7.4 Results

Participant 2 complained of abdominal discomfort after the pre-study assessment session (discussed in more detail in Section 7.5) and was removed from the study at this point. Their data was not used for analysis.

The results of a Shapiro-Wilk test showed that 21 (87.5%) of the unstimulated FVC data sets were normally distributed, validating the use of a parametric test for significance testing.

7.4.1 AFES Training

In this randomised crossover design, Participant 1 completed the training period before the control period, while Participants 3 and 4 completed the control period first. Participant 1's stimulated and unstimulated FVC, PEF and FEV₁, recorded at each of the eight assessment sessions, are shown in Figure 7.3, with the data recorded from Participants 3 and 4 shown in Appendix C. Participant 1's FVC and PEF increased over the study duration, while FEV₁ was found to be more variable.

Stimulated FVC was found to be clinically significantly greater than unstimulated FVC at five of the 24 (20.8%) assessment sessions and clinically significantly smaller at three of the 24 (12.5%) assessment sessions. Stimulated FVC increased clinically significantly during eight of the 21 (38.1%) combined fortnights of participation and decreased clinically significantly during three (14.3%) of the fortnights of participation. Of these increases, six (75.0%) occurred during AFES training, while one (33.3%) of the decreases occurred during AFES training. Unstimulated FVC was found to increase clinically significantly during nine (42.9%) of the 21 combined fortnights of participation and decrease clinically significantly during four (19.0%) of the fortnights of participation. Of these increases, eight (88.9%) occurred during AFES training, while two (50%) of the decreases occurred during AFES training.

The grouped changes in respiratory function over the 14 week study duration, as well as over the four week control and eight week AFES training periods, are shown in Table 7.3. All measures of respiratory function increased during the study. The effect size (see Section 3.5.4) for the changes over the entire study duration, as well as during the control and training

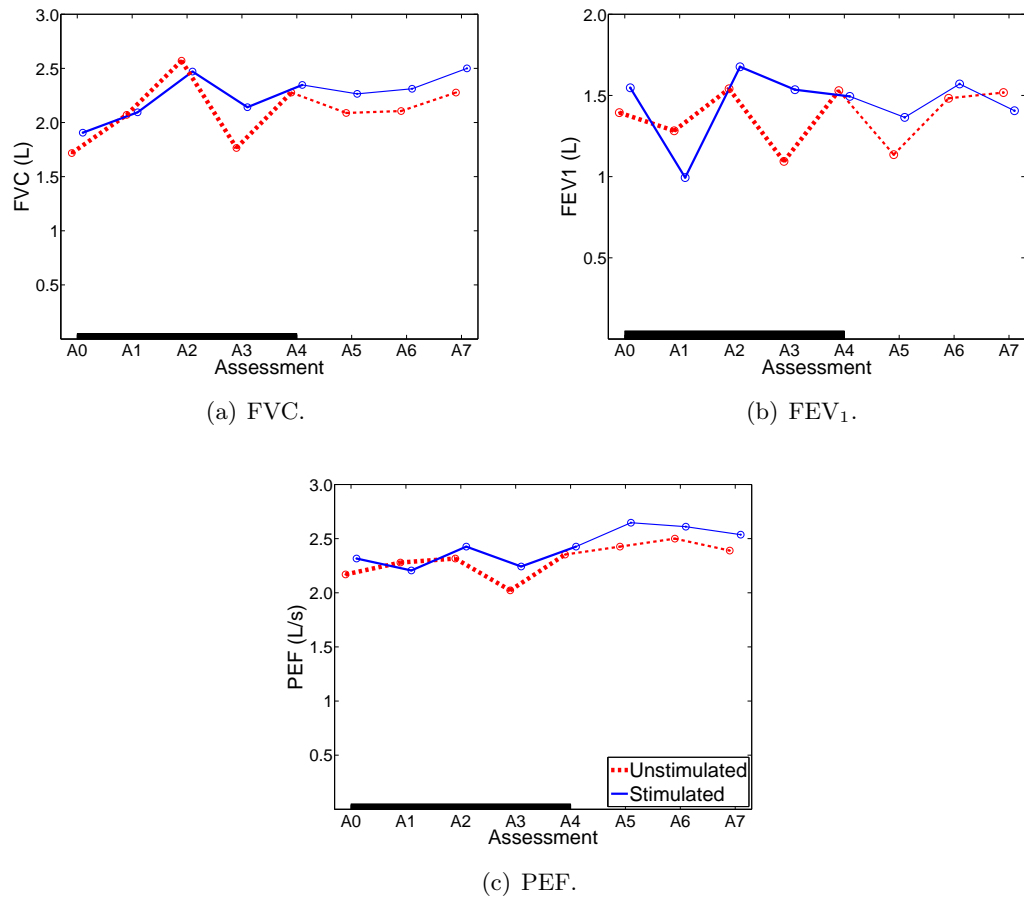


Figure 7.3: Forced Vital Capacity (FVC), Forced Exhaled Volume in one second (FEV₁) and Peak Expiratory Flow (PEF) of Participant 1 recorded at eight fortnightly assessment sessions, where a blue line represents stimulated, and a red line unstimulated, breaths. Solid black line along the bottom of the plot represents the eight week period of AFES training and no line indicates no training.

periods, is shown in Appendix C, with a large effect size observed for all measures. When taking into account the shorter (four week) control period, stimulated and unstimulated FVC/kg increased to a greater degree during the AFES training period than the control period, while stimulated and unstimulated PEF/kg and FEV₁/kg increased to a greater degree during the control period. None of the longitudinal changes in respiratory function observed over the whole study duration, over the control period or over the training period, were statistically significant. Due to the small number of participants who completed this study it was not possible to assess whether respiratory function plateaued within the study duration.

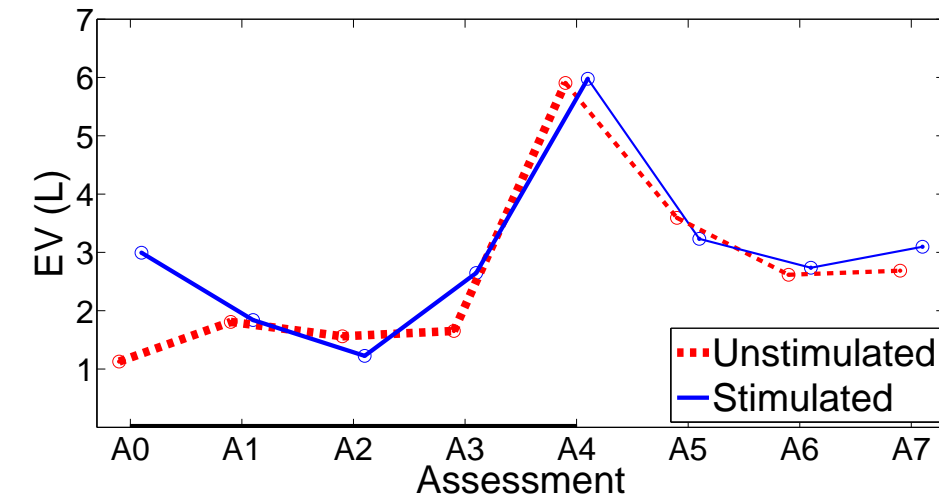
7.4.2 AFES with MI-E

Participant 1 also took part in eight MI-E assessment sessions. Figure 7.4 shows Participant 1's EV and PF recorded during unassisted and AFES assisted MI-E at each of the eight MI-E sessions.

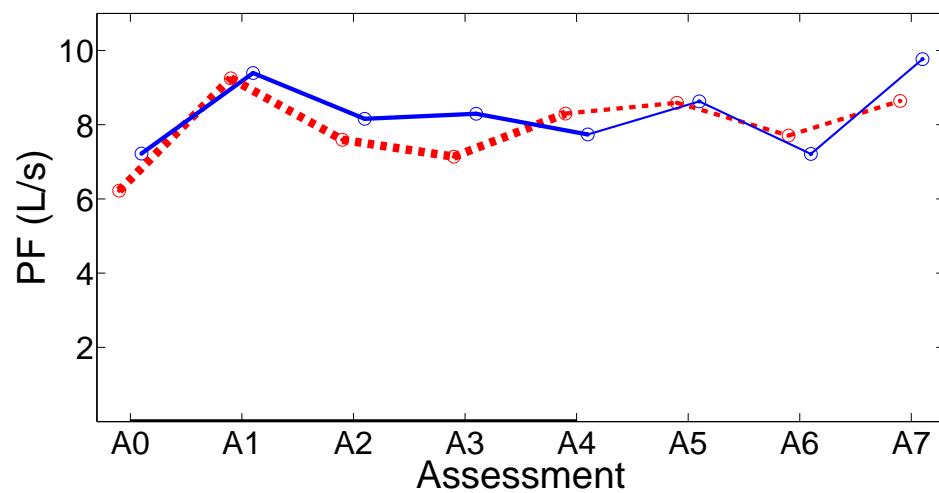
Table 7.3: Change (mean \pm standard deviation) in Stimulated (Stim) and Unstimulated (Unstim) Weight Corrected Forced Vital Capacity (FVC/kg), Weight Corrected Peak Expiratory Flow (PEF/kg) and Weight Corrected Forced Exhaled Volume in one second (FEV₁/kg), calculated from three participants, over the 14 week study duration, the eight week AFES training period and the four week control period. Results are presented as the absolute change and the change normalised per week for each period. Baseline values for each measurement are also given.

Variable	Stim	Baseline	Mean change over study	Mean change over control	Mean change over training
Absolute					
FVC/kg (mL/kg)	Stim	29.8 \pm 3.5	14.1 \pm 7.5	4.9 \pm 4.3	10.9 \pm 5.1
	Unstim	28.5 \pm 5.5	15.4 \pm 9.7	4.9 \pm 6.9	12.2 \pm 5.2
PEF/kg (mL/kg/s)	Stim	27.6 \pm 7.9	24.5 \pm 27.1	12.4 \pm 16.5	11.8 \pm 10.3
	Unstim	26.5 \pm 6.9	27.6 \pm 26.3	12.9 \pm 16.0	12.0 \pm 9.6
FEV ₁ /kg (mL/kg)	Stim	20.9 \pm 5.4	11.6 \pm 14.9	5.1 \pm 7.8	7.8 \pm 7.4
	Unstim	18.2 \pm 4.7	15.0 \pm 14.0	8.6 \pm 7.2	8.5 \pm 5.8
Normalised per week					
FVC/kg (mL/kg/week)	Stim	-	1.0 \pm 0.5	1.2 \pm 1.1	1.4 \pm 0.6
	Unstim	-	1.1 \pm 0.7	1.2 \pm 1.7	1.5 \pm 0.6
PEF/kg (mL/kg/s/week)	Stim	-	1.7 \pm 1.9	3.1 \pm 4.1	1.5 \pm 1.3
	Unstim	-	2.0 \pm 1.9	3.2 \pm 4.0	1.5 \pm 1.2
FEV ₁ /kg (mL/kg/week)	Stim	-	0.8 \pm 1.1	1.3 \pm 2.0	1.0 \pm 0.9
	Unstim	-	1.1 \pm 1.0	2.1 \pm 1.8	1.1 \pm 0.7

When comparing the results achieved with MI-E combined with AFES to those achieved with MI-E alone the application of AFES led to an acute increase in EV and PF at six of the eight (75%) assessment sessions. The results recorded at assessment four (A4) appeared to be outliers, with the EV and PF recorded at that assessment much greater than the results obtained at any other assessment session. However, these results did meet the repeatability criteria outlined in the ATS standards (see Section 3.2) and can therefore be assumed to have been recorded correctly.



(a) EV with MI-E



(b) PF with MI-E

Figure 7.4: Stimulated (blue) and unstimulated (red) Exhaled Volume (EV) and Peak Flow (PF) for Participant 1 over the 14 week study duration when using MI-E. The solid black line along the bottom of the plot indicates the eight week period of AFES training.

7.5 Discussion

The aims of this study were i) to evaluate the feasibility and effectiveness of an extended AFES training program to improve the respiratory function of sub-acute tetraplegic participants and ii) to evaluate the feasibility of combining AFES with MI-E.

While ethical approval to recruit 10 participants for this study has been granted four participants were recruited within the time frame of this thesis. Participant 2 withdrew from the study after the familiarisation session due to abdominal pain. It is believed this pain was caused by this participant's regular rehabilitation therapy, rather than the intervention applied here. Therefore, only three participants completed AFES training. Additionally, due to this time frame and a number of practical problems, AFES combined with MI-E was

only tested with one participant. These practical problems are discussed in further detail in Section 7.5.3.

7.5.1 AFES Training

The feasibility of using an extended AFES training program with the sub-acute tetraplegic population was demonstrated by the 100 percent compliance of the three participants to the training sessions.

Acute Effect AFES led to an acute, clinically significant (greater than 200 mL), increase in FVC at 21 percent of the assessment sessions.

Longitudinal Effect FVC, PEF and FEV₁ increased throughout the study, however only unstimulated FVC increased at a faster rate during the AFES training period than the control period. While this may suggest that the improvements in PEF and FEV₁ observed in this study can be attributed more to natural recovery than the training intervention, anomalies within this study could explain the apparent lack of training effect. As two of the three participants completed the control period before the training period, with natural recovery expected to be greatest in the early weeks of the study, the natural recovery observed during the control period may mask any training effect. This natural recovery was particularly evident in Participant 3 (see Appendix C) whose unstimulated FVC (45%), PEF (164%) and FEV₁ (128%) greatly increased during the control period before increasing to a lesser degree (FVC 28%, PEF 44% and FEV₁ 37%) during the intervention period. It was found that for Participant 1, who completed the AFES training period first, FVC, PEF and FEV₁ increased by 33, 8 and 10 percent during the intervention period and 9, -2 and 34 percent during the control period and for Participant 4, who completed the control period first, FVC, PEF and FEV₁ increased by 53, 48 and 29 percent during the intervention period and -2, 16 and 27 percent during the control period. These results, which show a greater increase in FVC and PEF during the intervention period than the control period, suggest that there may be a training effect from the intervention. The large increase in the respiratory function of Participant 3 over the control period may mask this training effect in the grouped data. The recruitment of additional participants is required to clarify the presence of this training effect.

McLachlan *et al.* [70] demonstrated that a three week AFES training program led to a statistically significant increase in FVC with 12 tetraplegic participants. In Chapter 6 a statistically significant increase in V_C was demonstrated over an eight week period, where AFES was applied on alternate weeks with nine acute, initially ventilator dependant, tetraplegic participants. In this study no statistically significant differences in longitudinal measures of respiratory function were found. This can be attributed to low participant numbers.

While stimulated and unstimulated FVC only increased by a clinically significant amount between 38 and 43 percent of the assessment sessions respectively, 75.0 and 88.9 percent of these improvements occurred during weeks when AFES training was applied. This suggests that while it is not always possible to achieve a clinically significant improvement in FVC in a two week period, the probability is greater when AFES training is applied. One motivation for this study was to establish the optimum duration for AFES training, denoted as the point at which respiratory function begins to plateau. Due to the small number of participants it was not possible to establish this optimum training duration.

Ethical approval has been granted for a total of 10 participants to take part in this study, however only four were recruited, and three completed the study, within the time frame of this thesis. The continuation of the study with an additional six participants may make it possible to demonstrate statistically significant gains in respiratory function over the AFES training period.

7.5.2 AFES with MI-E

The feasibility of combining AFES with MI-E was demonstrated by the successful integration of the technology at the eight MI-E sessions. At these assessment sessions it was possible to measure EV and PF during MI-E, with and without AFES. The results show that at 75 percent of the MI-E sessions stimulated EV and PF were greater than unstimulated EV and PF. This suggests that the addition of AFES to MI-E may provide an additional boost to cough power. This should lead to more effective secretion clearance compared to the application of MI-E alone. As AFES is non-invasive, the integration of AFES with MI-E is worth considering for all future uses of MI-E. The development of an inexpensive and practical AFES device, which can easily be synchronised with MI-E and used by a caregiver, would make this even more practical. The development of such a device is discussed in Section 8.5.

The EV and PF results recorded at MI-E session four (A4) were very different to the results recorded at all other MI-E and assessment sessions. The fact that these values met the ATS/ERS guidelines, and the fact the stimulated and unstimulated values are similar, suggest that this was not a measurement error. One possibility is that the MI-E device was on a different setting at this session compared to the other sessions. As the controls for this device are analogue it is difficult to guarantee the same pressures were applied at each MI-E session. It is also possible that the participant managed to form a different/better seal around the mouthpiece at this session, although it is unlikely this would cause such a large deviation in the results.

A large difference was observed between the PF measured with and without MI-E. This is attributed to the spirometer at the MI-E sessions measuring the PF produced by the MI-E device, rather than the PF generated by the participant. This is due to the large change in flow rate when MI-E alternates between positive and negative pressure. As the spirometer

needs to be placed in line with the MI-E tubing to accurately measure flow this can not be avoided. Therefore, a true measure of a persons PF can not be established when measuring PF from MI-E. Additionally, when measuring respiratory function the participant was unable to inhale to total lung capacity and exhale fully due to the short inhalation and exhalation duration used with an MI-E device. This means that a true measure of FVC can not be obtained when measuring the volume exhaled during MI-E.

7.5.3 Limitations and Future Work

One of the greatest challenges when conducting a study with the sub-acute tetraplegic population is effective patient selection. This is due to the vastly different rates of recovery and levels of respiratory function observed in this population. In this study the inclusion criteria was sub-acute tetraplegic patients with reduced respiratory function, as judged by a consultant at the QENSIU. However, due to the limited number of patients at the QENSIU, and a fear of excluding otherwise eligible participants, no quantitative measure of this reduction in respiratory function was used. If conducting a larger trial, with access to greater patient numbers, it may be worth considering the use of a quantitative measure of reduction in respiratory function to enable greater patient matching in this population. Such patient matching may reduce some of the intersubject variability in respiratory function observed in this study.

To fully compare the effectiveness of combining AFES with MI-E it would be desirable to also compare respiratory function during MI-E combined with manually assisted coughing (see Section 7.2). However, as the force required to successfully apply a manually assisted cough is subjective the same caregiver should apply all manually assisted coughs in a longitudinal study. Due to shift rotations it was not possible to have the same caregiver attend all assessment sessions in this study and a comparison between the use of AFES and manually assisted coughing with MI-E was not made.

Participant 2, who did not complete the study, had a large amount of edema in the abdomen which made it difficult to achieve a strong muscle contraction using AFES, requiring around 50 percent more current to achieve a visible muscle contraction compared to the other participants (see Table 7.2). This agrees with the findings in Chapter 6 and is discussed further in Section 8.4.

The effectiveness of combining AFES with MI-E was only assessed with one participant. This was for two reasons. Firstly, it was originally intended only to use MI-E with participants who were receiving this treatment as part of their regular rehabilitation. However, MI-E was only routinely being used in the QENSIU with ventilated patients, who were not included in this protocol. This meant that the device and experience of MI-E was unfamiliar for the participant in this study. The use of MI-E with participants who have experience using the device may improve the results. Secondly, the participant indicated that they did not feel

that they were always actively contributing during MI-E. As the feasibility of combining AFES with MI-E had been shown, and the novel use of a pressure sensor to automatically synchronise AFES with MI-E had been successfully demonstrated, no further assessments were carried out. A larger trial that measures the difference between FVC with AFES assisted and unassisted MI-E, and incorporates manually assisted coughing, may further demonstrate the effectiveness of this technique.

A further limitation of this study is that an FVC test, from which the results were derived, relies on the maximum effort of the participant. It is possible that participants did not make as much effort at certain assessment sessions, which may account for some of the variability observed in the results. Finally, a control period of four weeks and a training period of eight weeks were used in this study. These durations were chosen as it was felt that, based on the results observed by McLachlan *et al.* [70], a training period of eight weeks may lead to a plateau in respiratory function. Due to the small number of participants recruited in this study it was not possible to establish whether such a plateau had occurred. Although it would have been desirable to also have an eight week control period, it was highlighted at the study conception phase that this would have increased the study duration to 18 weeks, and would have led to some participants being discharged from the QENSIU before the final assessment sessions. Rather than have incomplete results, it was decided to shorten the duration of the control period. In further experiments it may be beneficial to increase the duration of the control period.

7.6 Conclusion

This study has shown that FVC, PEF and FEV_1 increase in the weeks after a spinal cord injury, with FVC increasing at a greater rate during an eight week AFES training program than during a four week control period. It was also shown that AFES could be combined with MI-E to generate an acute increase in respiratory function compared to MI-E alone. However, to show statistical significance, more participants are required.

Chapter 8

Discussion and Recommendations for Future Work

*“I think that in the discussion of natural problems we ought to begin not with the Scriptures,
but with experiments, and demonstrations.”*

Galileo Galilei

8.1 Summary

The main findings of this thesis are summarised in this chapter. An evaluation of the techniques and protocols developed to improve the effectiveness of Abdominal Functional Electrical Stimulation (AFES) in improving the respiratory function of people with tetraplegia is provided. This chapter also outlines possible future directions for research involving the use of AFES as a treatment modality. Important outstanding issues that require to be addressed before AFES becomes a standard clinical technique are discussed.

8.2 Evaluation of AFES to Improve Respiratory Function

The patients who would benefit most from the application of AFES have yet to be clearly identified. AFES is commonly used with any tetraplegic patient, however the response from patient to patient can vary significantly. The difference in response is further complicated by the lack of common protocol between AFES studies, especially with regard to electrode placement as described in Section 2.4.4.3. While motor point charts exist for many muscle groups [155], relatively little attention has been given to mapping the abdominal motor points. In Chapter 5 the use of Neuromuscular Electrical Stimulation (NMES) to establish the position of the motor points of the abdominal muscles is described. By using this technique the motor points of the abdominal muscles were quickly and easily detected in both able bodied and tetraplegic participants. These motor point positions were found to differ between participants, suggesting that empirically derived electrodes positions are too general to accurately target the motor points and achieve the optimum muscle contraction. In this study it was also established that the position of the motor points could be detected with good repeatability, suggesting that this technique only needs to be performed once for each user. If future AFES studies were to identify the motor points of the abdominal muscles using NMES, application of AFES at these motor points would help achieve the optimum muscle contraction. This should lead to the greatest improvement in respiratory function and should ensure a consistent electrode placement across studies. While the results achieved in different AFES studies is influenced by a wide range of factors, and is more complex than just ensuring that electrodes are placed in the same location, a consistent electrode placement will remove one variable for these studies, enabling an easier comparison.

8.2.1 Clinical Studies

In this thesis it has been shown that AFES is a feasible technique for use with acute ventilator dependant (see Chapter 6) and sub-acute, non-ventilator dependant, tetraplegic patients (see Chapter 7). It was also shown that AFES led to an acute and a longitudinal increase in respiratory function.

8.2.1.1 Acute Effect

In the two clinical studies conducted in this thesis, documented in Chapters 6 and 7, it was shown that the application of AFES led to an acute increase in Vital Capacity (V_C) and Forced Vital Capacity (FVC) compared to unassisted measurements. This agrees with Langbein *et al.* [71] and Lee *et al.* [122] who both found an acute increase in FVC during the application of AFES. In Chapter 6 it was also shown that the application of AFES led to an acute increase in Tidal Volume (V_T), agreeing with previous studies that also demonstrated acute improvements in V_T during the application of AFES [72, 120, 121]. This indicates that the use of AFES can lead to an immediate improvement in respiratory function. This could be beneficial for tetraplegic patients who require an acute improvement in respiratory function to aid cough generation or combat a respiratory infection.

It should be noted that results in Chapter 6 are expressed as V_C rather than FVC as, at early assessment sessions, participants could not always exhale as ‘forcibly as possible’ due to sedation levels and poor respiratory muscle coordination. However, as explained in Section 1.4.2, there is very little difference between the values of V_C and FVC. It should also be noted that for the purpose of these tests patients were assumed to be inhaling to the maximum lung volume that they could achieve, denoted as their functional lung capacity, rather than their total lung capacity which is typically used for an FVC and V_C manoeuvre with the able bodied population. Inhalation to functional lung capacity provided both a measure of the impairment of the respiratory muscles and the improvement in respiratory function over the study duration.

8.2.1.2 Longitudinal Effect

In Chapters 6 and 7, V_C and FVC were found to increase over the study duration, agreeing with previous studies that used an AFES training protocol with the tetraplegic population [70, 73, 124]. The increase in Peak Expiratory Flow (PEF) and Forced Exhaled Volume in one second (FEV_1) observed in Chapter 7 also agrees with these previous studies. The clinical studies described in Chapters 6 and 7 included control periods, used to estimate the effect of natural recovery. This was necessary as Liaw *et al.* [113] showed a statistically significant increase in FVC (27%) and FEV_1 (21%) over a six week period for tetraplegic (C4 to C7) participants who were less than six months post injury and received no intervention. While they also found an increase in PEF (23%), this was not statistically significant. These increases in FVC, FEV_1 and PEF are equivalent to 4.5, 3.5 and 3.8 percent per week. In Chapter 7 it was found that unstimulated FVC, FEV_1 and PEF increased by an average of 3.9, 5.9 and 7.4 percent per week and in Chapter 6 unstimulated V_C was found to increase by an average of six percent per week over the eight week study duration. While these results were found to vary from week to week and between participants, they suggest that the improvements in respiratory function reported in this thesis may be larger than those caused by natural recovery alone. However, it is difficult to effectively quantify the intervention effect

with the small number of participants recruited for the studies documented in this thesis. In clinical studies the most common way to estimate the effect of natural recovery during an intervention protocol is to conduct a Randomised Control Trial (RCT) which includes a control group, with the changes in the intervention and control groups compared. A number of issues surround the use of RCTs in studies that recruit patients with Spinal Cord Injury (SCI). Firstly, the large variations in function and recovery after SCI make it difficult to establish control and intervention groups that have similar characteristics, especially in the case of respiratory function. When conducting studies that involve an intervention, such as AFES, which has been shown to be potentially useful, and importantly not harmful, there is also an ethical concern as to whether denying the control group this treatment is ethically responsible. Therefore, RCTs may not be the most suitable design for studies in tetraplegia, with a randomised cross-over design (as used in Chapter 7) potentially more appropriate. Due to the low number of participants available for the studies documented in this thesis (see Section 8.4), each participant acted as their own control. By conducting similar multicentre studies, which would provide access to more participants, it may be possible to include a control group. Large scale clinical trials investigating the effect of AFES training on respiratory function have yet to be conducted, with the only such study conducted by Cheng *et al.* [124] recruiting only 13 participants for each of the intervention and control groups.

When investigating the effect of an extended AFES training program in Chapter 7, FVC was found to be the only measure of respiratory function that increased to a greater extent during an AFES training period than during the control period. As explained in Section 7.5, the respiratory function of one participant in this study improved significantly during the control period, with a much greater improvement in respiratory function during this period than observed for the other two participants who also completed this study. When comparing the group results it is possible that this participants large increase in respiratory function during the control period is masking any increase in respiratory function that was caused by the intervention. The recruitment of additional participants should clarify this effect. When applying AFES with acute ventilator dependent tetraplegia patients in the study documented in Chapter 6 V_T was found to increase over the study duration, although this change was not found to be statistically significant. Stimulated V_T was the only measure of respiratory function that was found to increase to a greater extent during weeks where AFES training was applied compared to control weeks. As explained in Section 6.6, the apparent lack of difference between intervention and control weeks may be caused by an acute carry over effect from AFES training, rather than a lack of an intervention effect. Further investigations will be required to quantify this carry over effect.

AFES training was found to lead to a clinically significant (greater than 200 mL) increase in stimulated and unstimulated FVC between 33.3 and 37.5 percent of assessment sessions in Chapter 7 and between 21.1 and 23.9 percent of assessment sessions in Chapter 6. In both studies the majority of these clinically significant increases in stimulated and unstimulated

FVC were found to occur during weeks where AFES training was applied (75.0 and 88.9 percent in Chapter 7 and 60.0 and 58.8 percent in Chapter 6). This provides another indication that there may be a positive longitudinal training effect from AFES with the tetraplegic population.

In Chapter 6 the use of an AFES training program with the acute ventilator dependant tetraplegic population was shown to decrease the time that the participants were dependant on mechanical ventilation by an average of 11 days compared to matched controls. While this study only recruited tetraplegic participants in the acute stage of injury, a single participant case study, also reported in Chapter 6, investigated the use of an AFES training program to assist a chronic tetraplegic participant to wean from mechanical ventilation. This case study demonstrated that AFES was a feasible technique for assisting chronic ventilator dependant tetraplegics, who retain some diaphragm function, in weaning from mechanical ventilation. The time this participant spent breathing independently of mechanical ventilation increased from zero minutes per day before a three week AFES training intervention, to 90 minutes per day after. While these results suggest that an AFES training program may be suitable to assist all tetraplegics who retain diaphragm function to wean from mechanical ventilation, further work is required to establish the effectiveness of this treatment modality with the chronic tetraplegic population.

8.2.1.3 Technological Aspects

In Chapter 4 it was shown that a respiratory effort belt positioned around the chest could be combined with a Support Vector Machine (SVM) algorithm to classify respiratory activity, with an acceptable classification performance compared to that achieved using the signal from a spirometer. The integration of this algorithm into an AFES device would allow the correct stimulation parameters for different breath types to be automatically applied at the correct point in the respiratory cycle. It was also shown in Chapter 4 that the signal from a respiratory effort belt positioned around the abdomen could be used to detect the start of exhalation at approximately the same time as when using the signal from a spirometer, indicating that this sensor could be used to automatically apply AFES at the correct point in the respiratory cycle. In Chapters 6 and 7 the respiratory effort belt used to detect respiratory activity had to be placed around the abdomen. This was because many acute tetraplegics require a halo or back brace to stabilise their SCI, limiting access to their chest. Therefore, the combination of a respiratory effort belt positioned around the chest with a SVM may not be a suitable method for classifying the respiratory activity of the acute tetraplegic population. Despite this, the signal from the respiratory effort belt positioned around the abdomen was used to automatically apply stimulation at the start of exhalation in Chapters 6 and 7, with high accuracy. For the clinical application of AFES training, where it can be assumed all breaths will be quiet breaths, the automatic application of AFES using the signal from a respiratory effort belt placed around the abdomen could be integrated into an automatic

AFES system.

Pressure ulcers, or pressure sores, develop when pressure is applied to the same area of skin over an extended period of time [170]. To avoid the development of pressure ulcers tetraplegic patients are normally turned in their bed every few hours, changing their centre of pressure. This meant that the respiratory effort belts used to record respiratory activity in the clinical studies documented in this thesis were applied with tetraplegic patients in a number of different positions, ranging from the patient lying on their pelvis through to the patient being in a fully supine position. While it was shown in Section 3.3.3.1 that the largest signal magnitude was observed when the respiratory effort belt was under the greatest displacement, the pre-processing methods employed (discussed in Section 3.3.2) led to a very low level of signal noise. Therefore, the position of the patient, and hence the position of the respiratory effort belt, did not affect its performance for the automatic application of AFES. The successful automatic application of AFES indicates that the patient's respiratory activity was detected successfully, no matter their position. The statistical classification algorithm, described in Chapter 4, relies on successful detection of respiratory activity. Therefore, it is believed that the patient position would not affect the classification performance of this algorithm. However, this hypothesis remains to be tested with tetraplegic participants.

Both of the clinical studies described in this thesis (Chapters 6 and 7) included the use of the motor point detection technique described in Chapter 5 to select the optimum electrode position. The inclusion of this technique in all AFES studies should achieve a consistent muscle contraction and enable an easier comparison of the effectiveness of the intervention. Positive findings in such studies would add support to the use of AFES as a standard clinical intervention.

In summary the use of AFES to improve the respiratory function of the tetraplegic patient group is non-invasive and easy to apply, making it suitable for a clinical setting. Further evidence of the effect of AFES on respiratory function is required before it becomes an accepted treatment modality.

8.2.2 Respiratory Complications

Of the 12 tetraplegic participants who received AFES training in this thesis, only one (8%) developed a respiratory complication (pneumonia). These participants were recruited in the acute or sub-acute stage of injury, with nine of these participants observed for eight weeks (mean 22 ± 12 days post injury [range 10 to 39 days]) and three observed for 14 weeks (mean 24 ± 4 days post injury [range 19 to 29 days]). This respiratory complication rate is much lower than that observed in other studies with the acute tetraplegic population. Fishburn *et al.* [79] reported that of 30 tetraplegic patients studied in the first 30 days post injury, 17 (57%) suffered from a respiratory complication while Jackson and Groomes [80] report that in the first six weeks after injury 175 of the 261 (67%) tetraplegic participants

studied suffered from a respiratory complication. While these studies began observing the participants slightly earlier than in this thesis, none of the participants recruited in this thesis had, to date of recruitment, developed a respiratory complication. The low numbers of respiratory complications reported here agrees with the finding of Cheng *et al.* [124] who observed a reduction in the number of respiratory infections after an AFES training program. This suggests that the improvements in respiratory function achieved using an AFES training protocol may be beneficial in preventing respiratory infection and subsequent respiratory complications. It should be noted that patients who were severely unwell were not recruited for the studies in this thesis, which may reduce the observed number of respiratory complications.

8.3 Clinical Significance

The results of this thesis have led to AFES shortly being introduced as a standard treatment to assist ventilator weaning for acute ventilator dependent tetraplegic participants at the Queen Elizabeth National Spinal Injuries Unit (QENSIU). The use of AFES to assist all chronic ventilator dependent tetraplegics who retain some diaphragm function to wean from mechanical ventilation is also being piloted. This clinical implementation makes use of some of the technology described in Chapter 4 and the motor point detection technique outlined in Chapter 5, as well as the clinical protocols developed in Chapters 6 and 7. The results in this thesis add further evidence to support the clinical introduction of AFES. Despite this, AFES continues to suffer from a poor clinical uptake. Reasons for this are discussed in Section 8.5.

8.4 Limitations of AFES in People With Tetraplegia

In many critically ill patients there is a marked increase in body water which leads to an increase in extra cellular fluid volume, termed edema [168]. A study by Harper *et al.* [171] showed that when using FES to induce a contraction of the wrist muscles, stimulation current had to be approximately doubled in the presence of edema. It is hypothesised that this increase is caused by edema decreasing the current density of the stimulation and, in turn, decreasing the amount of charge reaching the nerve. During the clinical studies documented in Chapters 6 and 7 three participants who had a large amount of edema in the abdomen were found to be poor responders to AFES. Harper *et al.* describe a significant lowering of the current required to induce a contraction in the presence of edema when pressure was applied to the stimulating electrodes. It is believed that this is because when pressure is applied to the electrodes it brings the nerve closer to the stimulating electrode, increasing the charge delivered to the nerve resulting in a greater muscle contraction. This finding was supported in the three poor responders in this thesis, with the application of pressure to the stimulating electrodes found to induce a muscle contraction at lower stimulation currents than when pressure was not applied. In the clinical study documented in Chapter 6 a stimulation current of approximately 100 mA was required to achieve a muscle contraction with the participant

who had edema. The neuromuscular stimulator used in this thesis is limited to 120 mA. Therefore, in the presence of edema a muscle contraction may not be able to be achieved in all patients, with the presence of adipose tissue heightening this effect. Additionally, such high stimulation currents are likely to activate the pain receptors in incomplete patients who retain sensation in the abdomen, resulting in the application of AFES being painful. The presence of abdominal edema may need to be considered as an exclusion criteria in future AFES studies.

For FES to initiate a muscle contraction the Lower Motor Neurons (LMNs), which carry motor information from the spinal cord to a muscle (see Section 1.3 for more information), must be intact. If the LMNs are not intact the pathway between the nerve and a muscle is damaged. This means that the nerve can no longer be electrically stimulated to cause a muscle contraction, with the muscle said to be denervated [51]. One participant in Chapter 6 was found to be a non responder to AFES. It was later discovered that this participant had LMN damage. As LMN damage is often difficult to detect in the acute stage of injury, and as function can sometimes return after time in SCI when the LMNs are not damaged (largely attributed to spinal shock), this participant was followed up for eight weeks, with AFES being applied on a weekly basis. Over this eight week period no abdominal muscle contraction was achieved when using AFES and the participant never recovered the ability to breathe independently of mechanical ventilation by the time they were discharged from hospital. With this participant the presence of LMN damage was not established until a considerable time after injury. Therefore, the use of LMN damage as an exclusion criteria for AFES studies with the acute tetraplegic population may not be practical. While there are stimulators available that can stimulate denervated muscle by stimulating the muscles directly [172], as opposed to the nerve, they have not been used to apply AFES in the case of LMN damage. This may be a potential solution for the use of AFES for patients with LMN damage.

It is well known that the use of Functional Electrical Stimulation (FES) leads to faster muscle fatigue than natural recruitment (see Section 1.5.1 for further explanation). To allow for the effect of abdominal muscle fatigue within the clinical studies outlined in this thesis, stimulation pulsewidth was increased manually by approximately 20 μ s per five minutes of AFES training. There is currently no automatic way to detect this fatigue in the context of an AFES system, meaning that an automatic AFES system would rely on either a manual intervention or time signal to increase pulsewidth. Al-Mulla *et al.* [173] suggest ultrasound or electromyography (EMG) signals combined with a statistical classification algorithm as a potential solution for the real-time detection of muscle fatigue. Spivak *et al.* [90] used an EMG signal from the respiratory muscles to automatically apply AFES during exhalation to assist coughing. It may be that this EMG signal changes over time due to muscle fatigue, and that a statistical classification algorithm, such as that developed in Chapter 4, could be used to automatically adjust stimulation pulsewidth to account for respiratory muscle fatigue

in the context of an AFES system.

One of the greatest challenges in this thesis was participant recruitment. As can be seen in Figure 8.1, recruitment of the 10 participants in Chapter 6 took 20 months, with large breaks in recruitment. This is a problem inherent with studies involving the SCI population. As outlined in Section 1.2.1 there are around 100 patients admitted to the QENSIU per year, with a low number of these patients requiring mechanical ventilation. Due to these patients having a large number of comorbidities and a poor state of health, coupled with the number of patients who only require ventilation for a few days, the recruitment rates seen in Chapter 6 were in line with expectation. The benefit of AFES may be further highlighted by greater participant recruitment. To achieve this it may be necessary to establish multicentre trials, as the patient numbers seen in single SCI units are insufficient for such studies.

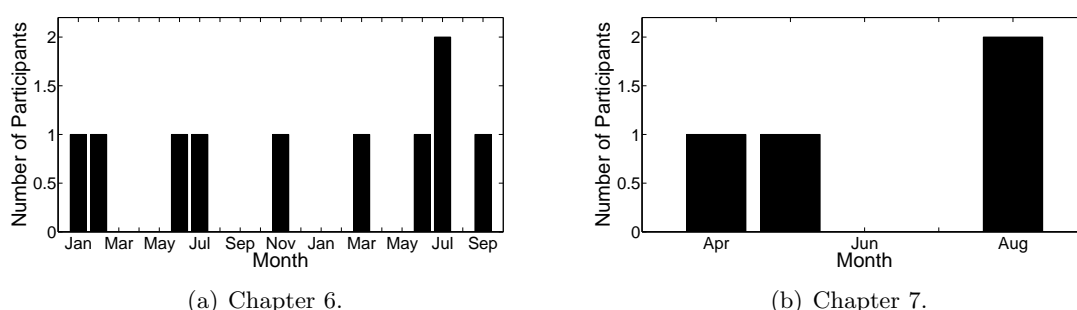


Figure 8.1: Participant recruitment for the studies reported in Chapter 6 and 7. Recruitment for the study reported in Chapter 6 started in January 2012 and recruitment for the study reported in Chapter 7 started in April 2013.

8.5 Future Work

“The inventor looks upon the world and is not contented with things as they are. He wants to improve whatever he sees, he wants to benefit the world; he is haunted by an idea. The spirit of invention possesses him, seeking materialization.”

Alexander Graham Bell

This thesis adds further support to the efficacy of AFES to improve respiratory function, yet the uptake of AFES with the tetraplegic population is still very low. While larger studies would add weight to support the use of AFES, the number of eligible participants for studies within any one spinal injuries unit is small, making the implementation of large studies within any one spinal injuries unit difficult. Collaborations in multicentre studies should lead to larger recruitment figures. After larger studies have been conducted that show the benefits of AFES, AFES may become a standard clinical procedure for the tetraplegic population. One problem with conducting such multicentre studies is ensuring all locations apply stimulation in the same way. This may be achieved by the steps outlined below.

8.5.1 Clinical Uptake of AFES

The lack of an easy to use clinical device, established clinical AFES protocols that allow a patient's regular caregiver to set up and use the system and a lack of clinical evidence are three major factors contributing to the poor clinical uptake of AFES and may be an important factor in the lack of multicentre AFES studies. The development of a statistical classifier that uses the signal from a non-intrusive sensor to distinguish between quiet breathing and coughing (see Chapter 4), allowing the appropriate stimulation parameters to be applied at the correct point in the breathing cycle, is a major step towards the development of a stand alone AFES device. In Chapter 5 it was shown that the position of the motor points of the abdominal muscles, around which it is desirable to place the stimulation electrodes, had a large intersubject variability. By using the technique described in Chapter 5 motor point positions can be found quickly, with the good repeatability of this method meaning that the positions of the motor points only require to be identified once for each user. A technique that ensures a consistent electrode placement is an important step towards the establishment of a clinical AFES protocol. Once the motor points have been detected it may be possible to develop a garment for each participant that allows electrodes to be positioned around the motor points, possibly by using velcro or buttons to attach the electrodes. The use of such a garment would avoid the time consuming process of donning and doffing electrodes, would avoid loose wires and would make the application of AFES much more compact. This garment could be integrated with a stand alone AFES device. Such a garment and device may enable the combination of AFES with mechanical ventilation (see Chapter 6) or Mechanical Insufflation-Exsufflation (MI-E) (see Chapter 7) as standard clinical practice. Effective clinical protocols for the use of AFES with acute ventilator dependent and sub-acute tetraplegic patients were demonstrated in Chapters 6 and 7, respectfully. A stand alone AFES device and effective AFES protocols should enable easier execution of multicentre trials, as all researchers would be using the same equipment, and would mean that, given proper training, AFES could be applied by nurses or physiotherapists as part of a regular care plan. This should increase the likelihood of AFES being adopted as a clinical intervention. The willingness of a company to develop such a system without the results from a multicentre study may make this difficult to achieve, meaning that a greater amount of clinical evidence may be needed before AFES becomes a standard clinical treatment for the tetraplegic population.

8.5.2 New Applications of AFES

The motivation for the use of AFES with the tetraplegic population has largely been that an improvement in respiratory function should lead to a reduction in respiratory infections and subsequent respiratory complications [70, 72, 73], a leading cause of rehospitalisation for this patient group. To date, Cheng *et al.* [124] are the only people to use an AFES training program to directly assess the impact of an AFES training program on the number of respiratory infections. While they did show a decrease in the number of respiratory infections

after an AFES training program, this was only evaluated in 13 treatment and 13 control patients. This effect may be further demonstrated by a large control study, with the number of respiratory infections developed by the control and intervention groups assessed to give an indication of the effectiveness of AFES in reducing respiratory infections, which, if proven, would add support to the adoption of AFES as a standard clinical treatment modality.

The use of FES as a treatment modality for critically ill, able bodied, patients in an intensive care unit is gaining interest, with a number of studies being conducted in the last few years [174]. In these studies FES has been applied to the muscles of the arms or the legs to prevent muscle atrophy and maintain muscle strength during periods of illness. The application of FES to the leg muscles of able bodied patients in an intensive care unit has been shown by Routsis *et al.* [125] to lead to faster weaning from mechanical ventilation, leading to a significant cost saving for the health care provider. The fact that the abdominal muscles are involved in respiration, whereas the muscles of the leg are not, might suggest that the application of AFES in the critically ill able bodied population may lead to faster weaning from mechanical ventilation. The large number of critically ill, able bodied, patients in an intensive care unit make it an ideal location to conduct a large RCT into the effectiveness of this intervention, yet, to date, no studies have used AFES with this patient group. Such a study may reveal a new and diverse area for AFES research.

In summary there are a number of areas in which the application and availability of AFES for the tetraplegic population can be developed. These developments should promote further research into the effectiveness of AFES with the tetraplegic population, which should further highlight the improvements in respiratory function that can be achieved using this treatment modality.

Chapter 9

Conclusions

“To succeed, jump as quickly at opportunities as you do at conclusions.”

Benjamin Franklin

This thesis describes the development and implementation of novel protocols and technologies designed to enhance the effectiveness of Abdominal Functional Electrical Stimulation (AFES) to improve the respiratory function of the tetraplegic population. The development of such technologies and protocols is required to allow AFES to be implemented as a treatment modality in the acute and sub-acute care setting. As such, a key contribution of this thesis is proof of feasibility.

One approach which would improve the effectiveness of AFES is the development of a stand alone AFES device, capable of stimulating different breath types with different stimulation parameters. As a first step towards this aim a non-intrusive respiratory effort belt positioned around the chest was used to record the respiratory activity of 10 able bodied participants. This signal was used to develop a novel support vector machine algorithm for non-intrusive real-time respiratory activity detection, which produced an acceptable classification performance compared to that achieved using the signal from a spirometer. It was also demonstrated that the signal from a respiratory effort belt could be used to apply stimulation at the correct point in the breathing cycle. The use of a non-intrusive sensor, coupled with an improved classification algorithm, improves on previous work, where the signal from an intrusive spirometer was used to detect and classify respiratory activity.

While it is known that when using electrical stimulation the optimum muscle contraction is achieved when stimulation is applied close to the motor point, current AFES studies use a range of empirically derived electrode positions to initiate a muscle contraction, with no consensus over the optimum electrode location. In this thesis a novel use of neuromuscular electrical stimulation to detect the position of the motor points of the abdominal muscles was developed. By applying single pulse electrical stimulation to the rectus abdominis and external oblique muscles, the position of the motor points of these muscles were successfully located in 10 able bodied and five tetraplegic participants. It was demonstrated that while motor point position changed little over time, they were posture dependent with a degree of intersubject variability. By using this new technique the motor points could be detected with an adequate repeatability. Placement of electrodes at the motor points found using this method is therefore believed to improve upon the use of empirically derived electrode locations and is recommend for all future AFES studies.

The feasibility of using AFES to improve the respiratory function of acute ventilator dependant tetraplegics is demonstrated in a clinical study. A novel AFES protocol, combined with novel engineering solutions to allow AFES to be synchronised with a mechanical ventilator or a user's respiratory activity, are presented. The respiratory function of nine tetraplegic participants increased throughout an eight week AFES training protocol. These gains in respiratory function suggest that these protocols are feasible for this patient group, indicating a new treatment group who may benefit from the use of AFES. It was also shown that the participants who received AFES training weaned from mechanical ventilation on

average 11 days faster than their matched controls. This suggests that the improvements in respiratory function achieved using this protocol may enable faster weaning from mechanical ventilation. The feasibility of using AFES to assist ventilator weaning for the chronic tetraplegic population who retain some diaphragm function is also demonstrated.

During the aforementioned clinical study it was observed that AFES appeared to lead to an increased demand for secretion clearance, necessary to avoid respiratory infections. This suggested that traditional methods of secretion loosening and clearance may be enhanced by combining them with AFES. To investigate this a novel engineering solution was developed to integrate Mechanical Insufflation-Exsufflation (MI-E) with AFES, and the feasibility of this integration demonstrated with one tetraplegic participant. The results show that the application of AFES led to an acute increase in respiratory function compared to when using MI-E alone, indicating that with further refinement of the protocol and technology the integration of these two treatment modalities could be used to more effectively remove secretions for people with tetraplegia.

Finally, the feasibility of using an eight week AFES training program to improve the respiratory function of people with tetraplegia is demonstrated. Respiratory function was shown to increase throughout the study duration, although further participant recruitment is required to clarify the effect of natural recovery in this increase. This training effect provides further evidence for the clinical use of an AFES training program to improve the respiratory function of tetraplegic participants.

In conclusion a number of novel technologies and protocols have been developed which can be used to enhance the effectiveness of AFES to improve the respiratory function of the tetraplegic population.

References

- [1] Christopher and Dana Reeve Foundation, *One Degree of Separation: Paralysis and Spinal Cord Injury in the United States*. Christopher and Dana Reeve Foundation, 2009.
- [2] D. J. Strauss, M. J. Devivo, D. R. Paculdo, and R. M. Shavelle, “Trends in life expectancy after spinal cord injury,” *Arch Phys Med Rehabil*, vol. 87, pp. 1079–1085, Aug 2006.
- [3] A. Ackery, C. Tator, and A. Krassioukov, “A global perspective on spinal cord injury epidemiology,” *J Neurotrauma*, vol. 21, pp. 1355–1370, Oct 2004.
- [4] Queen Elizabeth National Spinal Injuries Unit, *Annual Report 2011-12*. Queen Elizabeth National Spinal Injuries Unit, 2012.
- [5] J. E. Lasfargues, D. Custis, F. Morrone, J. Carswell, and T. Nguyen, “A model for estimating spinal cord injury prevalence in the United States,” *Paraplegia*, vol. 33, pp. 62–68, Feb 1995.
- [6] R. D. Adams and M. Salam-Adams, “Chronic nontraumatic diseases of the spinal cord,” *Neurol Clin*, vol. 9, pp. 605–623, Aug 1991.
- [7] E. Kay, A. Deutsch, D. Chen, L. Manheim, and D. Rowles, “Effects of etiology on inpatient rehabilitation outcomes in 65 to 74-year-old patients with incomplete paraplegia from a nontraumatic spinal cord injury,” *PMR*, vol. 2, pp. 504–513, Jun 2010.
- [8] National Spinal Cord Injury Statistical Center, *Complete public version of the 2011 annual statistical report for the spinal cord injured model systems*. National Spinal Cord Injury Statistical Center, 2011.
- [9] F. H. Geisler, W. P. Coleman, G. Grieco, D. Poonian, and Sygen Study Group, “Recruitment and early treatment in a multicenter study of acute spinal cord injury,” *Spine*, vol. 26, pp. S58–S67, Dec 2001.
- [10] J. F. Ravaud, M. Delcey, and J. F. Desert, “The Tetrafigap Survey on the long-term outcome of tetraplegic spinal cord injured persons, Part II: Demographic characteristics and initial cause of injury,” *Spinal Cord*, vol. 38, pp. 164–172, Mar 2000.

- [11] W. O. McKinley, R. T. Seel, and J. T. Hardman, "Nontraumatic spinal cord injury: Incidence, epidemiology and functional outcome.," *Arch Phys Med Rehabil*, vol. 80, pp. 619–623, Jun 1999.
- [12] M. E. L. van den Berg, J. M. Castellote, I. Mahillo-Fernandez, and J. de Pedro-Cuesta, "Incidence of nontraumatic spinal cord injury: A Spanish cohort study (1972-2008).," *Arch Phys Med Rehabil*, vol. 93, pp. 325–331, Feb 2012.
- [13] K. Ones, E. Yilmaz, A. Beydogan, O. Gultekin, and N. Caglar, "Comparison of functional results in non-traumatic and traumatic spinal cord injury.," *Disabil Rehabil*, vol. 29, pp. 1185–1191, Aug 2007.
- [14] S. C. Kirshblum, S. P. Burns, F. Biering-Sorensen, W. Donovan, D. E. Graves, A. Jha, M. Johansen, L. Jones, A. Krassioukov, M. J. Mulcahey, M. Schmidt-Read, and W. Waring, "International standards for neurological classification of spinal cord injury (Revised 2011).," *J Spinal Cord Med*, vol. 34, pp. 535–546, Nov 2011.
- [15] C. A. Angeli, V. R. Edgerton, Y. P. Gerasimenko, and S. J. Harkema, "Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans.," *Brain*, vol. 137, pp. 1394–1409, May 2014.
- [16] M. J. DeVivo, "Epidemiology of traumatic spinal cord injury: Trends and future implications.," *Spinal Cord*, vol. 50, pp. 365–372, May 2012.
- [17] S. Kirshblum, A. Botticello, D. P. Lammertse, R. J. Marino, A. E. Chiodo, and A. Jha, "The impact of sacral sensory sparing in motor complete spinal cord injury.," *Arch Phys Med Rehabil*, vol. 92, pp. 376–383, Mar 2011.
- [18] S. Berney, P. Bragge, C. Granger, H. Opdam, and L. Denehy, "The acute respiratory management of cervical spinal cord injury in the first 6 weeks after injury: A systematic review.," *Spinal Cord*, vol. 49, pp. 17–29, Jan 2011.
- [19] J. F. Ditunno, J. W. Little, A. Tessler, and A. S. Burns, "Spinal shock revisited: A four-phase model.," *Spinal Cord*, vol. 42, pp. 383–395, Jul 2004.
- [20] J. F. Ditunno and C. S. Formal, "Chronic spinal cord injury.," *N Engl J Med*, vol. 330, pp. 550–556, Feb 1994.
- [21] J. D. Houle and A. Tessler, "Repair of chronic spinal cord injury.," *Exp Neurol*, vol. 182, pp. 247–260, Aug 2003.
- [22] C. H. Ho, L. Wuermsier, M. M. Priebe, A. E. Chiodo, W. M. Scelza, and S. C. Kirshblum, "Spinal cord injury medicine. 1. Epidemiology and classification.," *Arch Phys Med Rehabil*, vol. 88, pp. S49–S54, Mar 2007.
- [23] G. DeJong and A. I. Batavia, "Toward a health services research capacity in spinal cord injury.," *Paraplegia*, vol. 29, pp. 373–389, Jul 1991.

- [24] S. J. T. Guilcher, B. C. Craven, M. A. McColl, L. Lemieux-Charles, T. Casciaro, and S. B. Jaglal, "Application of the Andersen's health care utilization framework to secondary complications of spinal cord injury: A scoping review.," *Disabil Rehabil*, vol. 34, no. 7, pp. 531–541, 2012.
- [25] C. Winslow, R. K. Bode, D. Felton, D. Chen, and P. R. Meyer, "Impact of respiratory complications on length of stay and hospital costs in acute cervical spine injury.," *Chest*, vol. 121, pp. 1548–1554, May 2002.
- [26] S. E. P. Munce, S. J. T. Guilcher, C. M. Couris, K. Fung, B. C. Craven, M. Verrier, and S. B. Jaglal, "Physician utilization among adults with traumatic spinal cord injury in Ontario: A population-based study.," *Spinal Cord*, vol. 47, pp. 470–476, Jun 2009.
- [27] S. Charlifue, D. Apple, S. P. Burns, D. Chen, J. P. Cuthbert, W. H. Donovan, D. P. Lammertse, M. A. Meade, and C. R. Pretz, "Mechanical ventilation, health, and quality of life following spinal cord injury.," *Arch Phys Med Rehabil*, vol. 92, pp. 457–463, Mar 2011.
- [28] W. O. McKinley, A. B. Jackson, D. D. Cardenas, and M. J. DeVivo, "Long-term medical complications after traumatic spinal cord injury: A regional model systems analysis.," *Arch Phys Med Rehabil*, vol. 80, pp. 1402–1410, Nov 1999.
- [29] C. P. Cardozo, "Respiratory complications of spinal cord injury.," *J Spinal Cord Med*, vol. 30, no. 4, pp. 307–308, 2007.
- [30] C. Winslow and J. Rozovsky, "Effect of spinal cord injury on the respiratory system.," *Am J Phys Med Rehabil*, vol. 82, pp. 803–814, Oct 2003.
- [31] P. W. New, H. B. Rawicki, and M. J. Bailey, "Nontraumatic spinal cord injury: Demographic characteristics and complications.," *Arch Phys Med Rehabil*, vol. 83, pp. 996–1001, Jul 2002.
- [32] E. Henneman, "Relation between size of neurons and their susceptibility to discharge.," *Science*, vol. 126, pp. 1345–1347, Dec 1957.
- [33] R. Jarosz, M. M. Littlepage, G. Creasey, and S. L. McKenna, "Functional electrical stimulation in spinal cord injury respiratory care.," *Top Spinal Cord Inj Rehabil*, vol. 18, no. 4, pp. 315–321, 2012.
- [34] A. F. DiMarco, "Restoration of respiratory muscle function following spinal cord injury. Review of electrical and magnetic stimulation techniques.," *Respir Physiol Neurobiol*, vol. 147, pp. 273–287, Jul 2005.
- [35] J. L. Hankinson, J. R. Odencrantz, and K. B. Fedan, "Spirometric reference values from a sample of the general U.S. population.," *Am J Respir Crit Care Med*, vol. 159, pp. 179–187, Jan 1999.

- [36] A. M. Spungen, W. A. Bauman, M. Lesser, and F. D. McCool, "Breathing pattern and ventilatory control in chronic tetraplegia.," *Lung*, vol. 187, no. 6, pp. 375–381, 2009.
- [37] G. Li, N. C. Arora, H. Xie, H. Ning, W. Lu, D. Low, D. Citrin, A. Kaushal, L. Zach, K. Camphausen, and R. W. Miller, "Quantitative prediction of respiratory tidal volume based on the external torso volume change: A potential volumetric surrogate.," *Phys Med Biol*, vol. 54, pp. 1963–1978, Apr 2009.
- [38] E. Atito-Narh, S. Pieri-Davies, and J. W. H. Watt, "Slow ventilator weaning after cervical spinal cord injury.," *Brit J Intensive Care*, vol. Autumn 2008, pp. 95–102, 2008.
- [39] W. P. Peterson, L. Barbalata, C. A. Brooks, K. A. Gerhart, D. C. Mellick, and G. G. Whiteneck, "The effect of tidal volumes on the time to wean persons with high tetraplegia from ventilators.," *Spinal Cord*, vol. 37, pp. 284–288, 1999.
- [40] S. H. Wilson, N. T. Cooke, R. H. Edwards, and S. G. Spiro, "Predicted normal values for maximal respiratory pressures in caucasian adults and children.," *Thorax*, vol. 39, pp. 535–538, Jul 1984.
- [41] D. Singh, R. Verma, R. K. Garg, M. K. Singh, R. Shukla, and S. K. Verma, "Assessment of respiratory functions by spirometry and phrenic nerve studies in patients of amyotrophic lateral sclerosis.," *J Neurol Sci*, vol. 306, pp. 76–81, Jul 2011.
- [42] A. E. Chiodo, W. Scelza, and M. Forchheimer, "Predictors of ventilator weaning in individuals with high cervical spinal cord injury.," *J Spinal Cord Med*, vol. 31, pp. 72–77, 2008.
- [43] K. E. Barrett, S. Boitano, S. M. Barman, and H. L. Brooks, *Ganongs Review of Medical Physiology*, 24e. McGraw-Hill Medical, 2012.
- [44] M. R. Miller, S. A. Dickinson, and D. J. Hitchings, "The accuracy of portable peak flow meters.," *Thorax*, vol. 47, pp. 904–909, Nov 1992.
- [45] D. M. Dryden, L. D. Saunders, B. H. Rowe, L. A. May, N. Yiannakoulis, L. W. Svenson, D. P. Schopflocher, and D. C. Voaklander, "Utilization of health services following spinal cord injury: A 6-year follow-up study.," *Spinal Cord*, vol. 42, pp. 513–525, Sep 2004.
- [46] J. F. Dasta, T. P. McLaughlin, S. H. Mody, and C. T. Piech, "Daily cost of an intensive care unit day: The contribution of mechanical ventilation.," *Crit Care Med*, vol. 33, pp. 1266–1271, Jun 2005.
- [47] J. J. Como, E. R. H. Sutton, M. McCunn, R. P. Dutton, S. B. Johnson, B. Aarabi, and T. M. Scalea, "Characterizing the need for mechanical ventilation following cervical spinal cord injury with neurologic deficit.," *J Trauma*, vol. 59, pp. 912–916, Oct 2005.
- [48] K. D. Anderson, "Targeting recovery: Priorities of the spinal cord-injured population.," *J Neurotrauma*, vol. 21, pp. 1371–1383, Oct 2004.

- [49] D. N. Rushton, "Functional electrical stimulation.," *Physiol Meas*, vol. 18, pp. 241–275, Nov 1997.
- [50] W. T. Liberson, H. J. Holmquest, D. Scot, and M. Dow, "Functional electrotherapy: Stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients.," *Arch Phys Med Rehabil*, vol. 42, pp. 101–105, Feb 1961.
- [51] L. R. Sheffler and J. Chae, "Neuromuscular electrical stimulation in neurorehabilitation.," *Muscle Nerve*, vol. 35, pp. 562–590, May 2007.
- [52] M. Gobbo, P. Gaffurini, L. Bissolotti, F. Esposito, and C. Orizio, "Transcutaneous neuromuscular electrical stimulation: Influence of electrode positioning and stimulus amplitude settings on muscle response.," *Eur J Appl Physiol*, vol. 111, pp. 2451–2459, Oct 2011.
- [53] M. Gobbo, N. A. Maffiuletti, C. Orizio, and M. A. Minetto, "Muscle motor point identification is essential for optimizing neuromuscular electrical stimulation use.," *J Neuroeng Rehabil*, vol. 11:17, 2014.
- [54] R. B. Szlavik and H. de Bruin, "The effect of stimulus current pulse width on nerve fiber size recruitment patterns.," *Med Eng Phys*, vol. 21, no. 6-7, pp. 507–515, 1999.
- [55] C. S. Bickel, C. M. Gregory, and J. C. Dean, "Motor unit recruitment during neuromuscular electrical stimulation: A critical appraisal.," *Eur J Appl Physiol*, vol. 111, pp. 2399–2407, Oct 2011.
- [56] J. S. Knutson, G. G. Naples, P. H. Peckham, and M. W. Keith, "Electrode fracture rates and occurrences of infection and granuloma associated with percutaneous intramuscular electrodes in upper-limb functional electrical stimulation applications.," *J Rehabil Res Dev*, vol. 39, no. 6, pp. 671–683, 2002.
- [57] P. N. Taylor, J. H. Burridge, A. L. Dunkerley, D. E. Wood, J. A. Norton, C. Singleton, and I. D. Swain, "Clinical use of the Odstock dropped foot stimulator: Its effect on the speed and effort of walking.," *Arch Phys Med Rehabil*, vol. 80, pp. 1577–1583, Dec 1999.
- [58] J. Chae and R. Hart, "Intramuscular hand neuroprosthesis for chronic stroke survivors.," *Neurorehabil Neural Repair*, vol. 17, pp. 109–117, Jun 2003.
- [59] P. H. Peckham, M. W. Keith, and A. A. Freehafer, "Restoration of functional control by electrical stimulation in the upper extremity of the quadriplegic patient.," *J Bone Joint Surg Am*, vol. 70, pp. 144–148, Jan 1988.
- [60] S. Y. Lee, S. Kang, S. H. Im, B. R. Kim, S. M. Kim, H. M. Yoon, and E. Y. Han, "The effects of assisted ergometer training with a functional electrical stimulation on exercise capacity and functional ability in subacute stroke patients.," *Ann Rehabil Med*, vol. 37, pp. 619–627, Oct 2013.

- [61] N. A. Hamzaid, K. R. Pithon, R. M. Smith, and G. M. Davis, "Functional electrical stimulation elliptical stepping versus cycling in spinal cord-injured individuals.," *Clin Biomech*, vol. 27, pp. 731–737, Aug 2012.
- [62] M. Valls, A. Rodriguez, A. Borau, and F. Mearin, "Effect of sacral anterior root stimulator on bowel dysfunction in patients with spinal cord injury.," *Dis Colon Rectum*, vol. 52, pp. 986–992, May 2009.
- [63] G. Lombardi, S. Musco, M. Celso, A. Ierardi, F. Nelli, F. D. Corso, and G. D. Popolo, "Intravesical electrostimulation versus sacral neuromodulation for incomplete spinal cord patients suffering from neurogenic non-obstructive urinary retention.," *Spinal Cord*, vol. 51, pp. 571–578, Jul 2013.
- [64] W. W. Glenn, W. G. Holcomb, R. K. Shaw, J. F. Hogan, and K. R. Holschuh, "Long-term ventilatory support by diaphragm pacing in quadriplegia.," *Ann Surg*, vol. 183, pp. 566–577, May 1976.
- [65] A. F. DiMarco, R. P. Onders, K. E. Kowalski, M. E. Miller, S. Ferek, and J. T. Mortimer, "Phrenic nerve pacing in a tetraplegic patient via intramuscular diaphragm electrodes.," *Am J Respir Crit Care Med*, vol. 166, pp. 1604–1606, Dec 2002.
- [66] R. P. Onders, "Functional electrical stimulation: Restoration of respiratory function.," *Handb Clin Neurol*, vol. 109, pp. 275–282, 2012.
- [67] A. F. DiMarco, K. E. Kowalski, R. T. Geertman, and D. R. Hromyak, "Lower thoracic spinal cord stimulation to restore cough in patients with spinal cord injury: Results of a national institutes of health-sponsored clinical trial. Part I: Methodology and effectiveness of expiratory muscle activation.," *Arch Phys Med Rehabil*, vol. 90, pp. 717–725, May 2009.
- [68] A. F. DiMarco, K. E. Kowalski, R. T. Geertman, D. R. Hromyak, F. S. Frost, G. H. Creasey, and G. A. Nemunaitis, "Lower thoracic spinal cord stimulation to restore cough in patients with spinal cord injury: Results of a national institutes of health-sponsored clinical trial. Part II: Clinical outcomes.," *Arch Phys Med Rehabil*, vol. 90, pp. 726–732, May 2009.
- [69] V. W. Lin, C. Hsieh, I. N. Hsiao, and J. Canfield, "Functional magnetic stimulation of expiratory muscles: A noninvasive and new method for restoring cough.," *J Appl Physiol*, vol. 84, pp. 1144–1150, Apr 1998.
- [70] A. J. McLachlan, A. N. McLean, D. B. Allan, and H. Gollee, "Changes in pulmonary function measures following a passive abdominal functional electrical stimulation training program.," *J Spinal Cord Med*, vol. 36, no. 2, pp. 97–103, 2013.
- [71] W. E. Langbein, C. Maloney, F. Kandare, U. Stanic, B. Nemchausky, and R. J. Jaeger, "Pulmonary function testing in spinal cord injury: Effects of abdominal muscle stimulation.," *J Rehabil Res Dev*, vol. 38, pp. 591–597, Sep-Oct 2001.

- [72] H. Gollee, K. J. Hunt, D. B. Allan, M. H. Fraser, and A. N. McLean, "A control system for automatic electrical stimulation of abdominal muscles to assist respiratory function in tetraplegia.," *Med Eng Phys*, vol. 29, pp. 799–807, Sep 2007.
- [73] R. A. McBain, C. L. Boswell-Ruys, B. B. Lee, S. C. Gandevia, and J. E. Butler, "Abdominal muscle training can enhance cough after spinal cord injury.," *Neurorehabil Neural Repair*, vol. 27, pp. 834–43, Jul 2013.
- [74] W. S. Linn, R. H. Adkins, H. Gong, and R. L. Waters, "Pulmonary function in chronic spinal cord injury: A cross-sectional survey of 222 southern California adult outpatients.," *Arch Phys Med Rehabil*, vol. 81, pp. 757–763, Jun 2000.
- [75] A. Baydur, R. H. Adkins, and J. Milic-Emili, "Lung mechanics in individuals with spinal cord injury: Effects of injury level and posture.," *J Appl Physiol*, vol. 90, pp. 405–411, Feb 2001.
- [76] S. Thomaz, P. Beraldo, S. Mateus, T. Horan, and J. C. Leal, "Effects of partial isothermic immersion on the spirometry parameters of tetraplegic patients.," *Chest*, vol. 128, pp. 184–189, Jul 2005.
- [77] W. S. Linn, A. M. Spungen, H. Gong, R. H. Adkins, W. A. Bauman, and R. L. Waters, "Forced vital capacity in two large outpatient populations with chronic spinal cord injury.," *Spinal Cord*, vol. 39, pp. 263–268, May 2001.
- [78] M. S. Call, M. E. Kutcher, R. A. Izenberg, T. Singh, and M. J. Cohen, "Spinal cord injury: Outcomes of ventilatory weaning and extubation.," *J Trauma*, vol. 71, pp. 1673–1679, Dec 2011.
- [79] M. J. Fishburn, R. J. Marino, and J. F. Ditunno, "Atelectasis and pneumonia in acute spinal cord injury.," *Arch Phys Med Rehabil*, vol. 71, pp. 197–200, Mar 1990.
- [80] A. B. Jackson and T. E. Groomes, "Incidence of respiratory complications following spinal cord injury.," *Arch Phys Med Rehabil*, vol. 75, pp. 270–275, Mar 1994.
- [81] P. C. Gay, "Counterpoint: Should phrenic nerve stimulation be the treatment of choice for spinal cord injury? No.," *Chest*, vol. 143, pp. 1203–1206, May 2013.
- [82] A. R. Claxton, D. T. Wong, F. Chung, and M. G. Fehlings, "Predictors of hospital mortality and mechanical ventilation in patients with cervical spinal cord injury.," *Can J Anaesth*, vol. 45, pp. 144–149, Feb 1998.
- [83] J. R. Ledsome and J. M. Sharp, "Pulmonary function in acute cervical cord injury.," *Am Rev Respir Dis*, vol. 124, pp. 41–44, Jul 1981.
- [84] M. J. Tobin, "Advances in mechanical ventilation.," *N Engl J Med*, vol. 344, pp. 1986–1996, Jun 2001.

- [85] J. S. Krause, M. J. Devivo, and A. B. Jackson, "Health status, community integration, and economic risk factors for mortality after spinal cord injury.," *Arch Phys Med Rehabil*, vol. 85, pp. 1764–1773, Nov 2004.
- [86] A. Esteban, F. Frutos, M. J. Tobin, I. Ala, J. F. Solsona, I. Valverd, R. Fernndez, M. A. de la Cal, S. Benito, and R. Toms, "A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group.," *N Engl J Med*, vol. 332, pp. 345–350, Feb 1995.
- [87] A. D. Martin, P. D. Davenport, A. C. Franceschi, and E. Harman, "Use of inspiratory muscle strength training to facilitate ventilator weaning: A series of 10 consecutive patients.," *Chest*, vol. 122, pp. 192–196, Jul 2002.
- [88] R. J. Jaeger, R. M. Turba, G. M. Yarkony, and E. J. Roth, "Cough in spinal cord injured patients: Comparison of three methods to produce cough.," *Arch Phys Med Rehabil*, vol. 74, pp. 1358–1361, Dec 1993.
- [89] S. H. Linder, "Functional electrical stimulation to enhance cough in quadriplegia.," *Chest*, vol. 103, pp. 166–169, Jan 1993.
- [90] E. Spivak, O. Keren, D. Niv, J. Levental, F. Steinberg, D. Barak, B. Chen, A. Zupan, and A. Catz, "Electromyographic signal-activated functional electrical stimulation of abdominal muscles: The effect on pulmonary function in patients with tetraplegia.," *Spinal Cord*, vol. 45, pp. 491–495, Jul 2007.
- [91] P. Sivasothy, L. Brown, I. E. Smith, and J. M. Shneerson, "Effect of manually assisted cough and mechanical insufflation on cough flow of normal subjects, patients with chronic obstructive pulmonary disease COPD, and patients with respiratory muscle weakness.," *Thorax*, vol. 56, pp. 438–444, Jun 2001.
- [92] J. R. Bach, "Mechanical insufflation-exsufflation. Comparison of peak expiratory flows with manually assisted and unassisted coughing techniques.," *Chest*, vol. 104, pp. 1553–1562, Nov 1993.
- [93] J. Sancho, E. Servera, P. Vergara, and J. Marn, "Mechanical insufflation-exsufflation vs. tracheal suctioning via tracheostomy tubes for patients with amyotrophic lateral sclerosis: A pilot study.," *Am J Phys Med Rehabil*, vol. 82, pp. 750–753, Oct 2003.
- [94] A. C. Tzeng and J. R. Bach, "Prevention of pulmonary morbidity for patients with neuromuscular disease.," *Chest*, vol. 118, pp. 1390–1396, Nov 2000.
- [95] M. R. Goncalves, T. Honrado, J. C. Winck, and J. A. Paiva, "Effects of mechanical insufflation-exsufflation in preventing respiratory failure after extubation: A randomized controlled trial.," *Crit Care*, vol. 16, p. R48, Mar 2012.

- [96] S. V. Garstang, S. C. Kirshblum, and K. E. Wood, "Patient preference for in-exsufflation for secretion management with spinal cord injury.," *J Spinal Cord Med*, vol. 23, no. 2, pp. 80–85, 2000.
- [97] A. F. DiMarco, "Diaphragm pacing in patients with spinal cord injury.," *Top Spinal Cord Inj Rehabil*, vol. 5, pp. 6–20, 1999.
- [98] J. P. Judson and W. W. Glenn, "Radio-frequency electrophrenic respiration. Long-term application to a patient with primary hypoventilation.," *JAMA*, vol. 203, no. 12, pp. 1033–1037, 1968.
- [99] W. W. Glenn, W. G. Holcomb, A. J. McLaughlin, J. M. O'Hare, J. F. Hogan, and R. Yasuda, "Total ventilatory support in a quadriplegic patient with radiofrequency electrophrenic respiration.," *N Engl J Med*, vol. 286, pp. 513–516, Mar 1972.
- [100] L. F. Wolfe, "Point: Should phrenic nerve stimulation be the treatment of choice for spinal cord injury? Yes.," *Chest*, vol. 143, pp. 1201–1203, May 2013.
- [101] A. Esclarn, P. Bravo, O. Arroyo, J. Mazaira, H. Garrido, and M. A. Alcaraz, "Tracheostomy ventilation versus diaphragmatic pacemaker ventilation in high spinal cord injury.," *Paraplegia*, vol. 32, pp. 687–693, Oct 1994.
- [102] A. F. DiMarco, "Neural prostheses in the respiratory system.," *J Rehabil Res Dev*, vol. 38, no. 6, pp. 601–607, 2001.
- [103] W. W. Glenn, J. F. Hogan, J. S. Loke, T. E. Ciesielski, M. L. Phelps, and R. Rowedder, "Ventilatory support by pacing of the conditioned diaphragm in quadriplegia.," *N Engl J Med*, vol. 310, pp. 1150–1155, May 1984.
- [104] M. L. Tedde, R. P. Onders, M. J. Teixeira, S. G. Lage, G. Ballester, M. W. I. Brotto, E. M. Okumura, and F. B. Jatene, "Electric ventilation: Indications for and technical aspects of diaphragm pacing stimulation surgical implantation.," *J Bras Pneumol*, vol. 38, no. 5, pp. 566–572, 2012.
- [105] R. P. Onders, S. Khansarinia, T. Weiser, C. Chin, E. Hungness, N. Soper, A. Dehoyos, T. Cole, and C. Ducko, "Multicenter analysis of diaphragm pacing in tetraplegics with cardiac pacemakers: positive implications for ventilator weaning in intensive care units.," *Surgery*, vol. 148, pp. 893–897, Oct 2010.
- [106] A. F. DiMarco, R. P. Onders, A. I., K. E. Kowalski, and J. T. Mortimer, "Phrenic nerve pacing via intramuscular diaphragm electrodes in tetraplegic subjects.," *Chest*, vol. 127, pp. 671–678, Feb 2005.
- [107] W. D. Man, J. Moxham, and M. I. Polkey, "Magnetic stimulation for the measurement of respiratory and skeletal muscle function.," *Eur Respir J*, vol. 24, pp. 846–860, Nov 2004.

- [108] M. I. Polkey, Y. Luo, R. Guleria, C. H. Hamnegrd, M. Green, and J. Moxham, "Functional magnetic stimulation of the abdominal muscles in humans.," *Am J Respir Crit Care Med*, vol. 160, pp. 513–522, Aug 1999.
- [109] T. Similowski, C. Straus, V. Attali, A. Duguet, B. Jourdain, and J. P. Derenne, "Assessment of the motor pathway to the diaphragm using cortical and cervical magnetic stimulation in the decision-making process of phrenic pacing.," *Chest*, vol. 110, pp. 1551–1557, Dec 1996.
- [110] A. F. DiMarco, G. S. Supinski, J. A. Petro, and Y. Takaoka, "Evaluation of intercostal pacing to provide artificial ventilation in quadriplegics.," *Am J Respir Crit Care Med*, vol. 150, pp. 934–940, Oct 1994.
- [111] A. F. DiMarco, Y. Takaoka, and K. E. Kowalski, "Combined intercostal and diaphragm pacing to provide artificial ventilation in patients with tetraplegia.," *Arch Phys Med Rehabil*, vol. 86, pp. 1200–1207, Jun 2005.
- [112] A. F. DiMarco and K. E. Kowalski, "Activation of inspiratory muscles via spinal cord stimulation.," *Respir Physiol Neurobiol*, vol. 189, pp. 438–449, Nov 2013.
- [113] M. Liaw, M. Lin, P. Cheng, M. A. Wong, and F. Tang, "Resistive inspiratory muscle training: Its effectiveness in patients with acute complete cervical cord injury.," *Arch Phys Med Rehabil*, vol. 81, pp. 752–756, 2000.
- [114] A. Zupan, R. Savrin, T. Erjavec, A. Kralj, T. Karcnik, T. Skorjanc, H. Benko, and P. Obreza, "Effects of respiratory muscle training and electrical stimulation of abdominal muscles on respiratory capabilities in tetraplegic patients.," *Spinal Cord*, vol. 35, pp. 540–545, Aug 1997.
- [115] S. V. Houtte, Y. Vanlandewijck, and R. Gosselink, "Respiratory muscle training in persons with spinal cord injury: A systematic review.," *Respir Med*, vol. 100, pp. 1886–1895, Nov 2006.
- [116] K. Stiller and N. Huff, "Respiratory muscle training for tetraplegic patients: A literature review.," *Aust J Physiother*, vol. 45, no. 4, pp. 291–299, 1999.
- [117] A. F. DiMarco, K. E. Kowalski, R. T. Geertman, and D. R. Hromyak, "Spinal cord stimulation: A new method to produce an effective cough in patients with spinal cord injury.," *Am J Respir Crit Care Med*, vol. 173, pp. 1386–1389, Jun 2006.
- [118] J. E. Butler, J. Lim, R. B. Gorman, C. Boswell-Ruys, J. P. Saboisky, B. B. Lee, and S. C. Gandevia, "Posterolateral surface electrical stimulation of abdominal expiratory muscles to enhance cough in spinal cord injury.," *Neurorehabil Neural Repair*, vol. 25, pp. 158–167, Feb 2011.

- [119] P. N. Taylor, A. M. Tromans, K. R. Harris, and I. D. Swain, "Electrical stimulation of abdominal muscles for control of blood pressure and augmentation of cough in a C3/4 level tetraplegic.," *Spinal Cord*, vol. 40, pp. 34–36, Jan 2002.
- [120] J. Sorli, F. Kandare, R. J. Jaeger, and U. Stanic, "Ventilatory assistance using electrical stimulation of abdominal muscles.," *IEEE Trans Rehabil Eng*, vol. 4, pp. 1–6, Mar 1996.
- [121] U. Stanic, F. Kandare, R. Jaeger, and J. Sorli, "Functional electrical stimulation of abdominal muscles to augment tidal volume in spinal cord injury.," *IEEE Trans Rehabil Eng*, vol. 8, no. 1, pp. 30–34, 2000.
- [122] B. B. Lee, C. Boswell-Ruys, J. E. Butler, and S. C. Gandevia, "Surface functional electrical stimulation of the abdominal muscles to enhance cough and assist tracheostomy decannulation after high-level spinal cord injury.," *J Spinal Cord Med*, vol. 31, no. 1, pp. 78–82, 2008.
- [123] F. Kandare, G. Exner, J. Jeraj, A. Aliverti, R. Dellaca, U. Stanic, A. Pedotti, and R. Jaeger, "Breathing induced by abdominal muscle stimulation in individuals without spontaneous ventilation.," *Neuromodulation*, vol. 5, pp. 180–185, Jul 2002.
- [124] P. Cheng, C. Chen, C. Wang, and C. Chung, "Effect of neuromuscular electrical stimulation on cough capacity and pulmonary function in patients with acute cervical cord injury.," *J Rehab Med*, vol. 38, no. 1, pp. 32–36, 2006.
- [125] C. Routsis, V. Gerovasili, I. Vasileiadis, E. Karatzanos, T. Pitsolis, E. Tripodaki, V. Markaki, D. Zervakis, and S. Nanas, "Electrical muscle stimulation prevents critical illness polyneuromyopathy: A randomized parallel intervention trial.," *Crit Care*, vol. 14, no. 2, p. R74, 2010.
- [126] J. Lim, R. B. Gorman, J. P. Saboisky, S. C. Gandevia, and J. E. Butler, "Optimal electrode placement for noninvasive electrical stimulation of human abdominal muscles.," *J Appl Physiol*, vol. 102, pp. 1612–1617, Apr 2007.
- [127] H. Gollee, K. J. Hunt, D. B. Allan, M. H. Fraser, and A. N. McLean, "Automatic electrical stimulation of abdominal wall muscles increases tidal volume and cough peak flow in tetraplegia.," *Technol Health Care*, vol. 16, no. 4, pp. 273–281, 2008.
- [128] A. Botter, G. Oprandi, F. Lanfranco, S. Allasia, N. A. Maffiuletti, and M. A. Minetto, "Atlas of the muscle motor points for the lower limb: Implications for electrical stimulation procedures and electrode positioning.," *Eur J Appl Physiol*, vol. 111, pp. 2461–2471, Oct 2011.
- [129] M. R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, R. Crapo, P. Enright, C. P. M. van der Grinten, P. Gustafsson, R. Jensen, D. C. Johnson, N. MacIntyre, R. McKay, D. Navajas, O. F. Pedersen, R. Pellegrino, G. Viegi, J. Wanger, and A. T. Force, "Standardisation of spirometry.," *Eur Respir J*, vol. 26, pp. 319–338, Aug 2005.

- [130] A. Kelley, E. Garshick, E. R. Gross, S. L. Lieberman, C. G. Tun, and R. Brown, "Spirometry testing standards in spinal cord injury.," *Chest*, vol. 123, pp. 725–730, Mar 2003.
- [131] E. J. McCaughey and H. Gollee, "A statistical classifier of breathing patterns for automatic abdominal muscle stimulation.," *In: Proceedings of 2nd Ann Conf of IFESS UKROI*, 2011.
- [132] C. Cortes and V. Vapnik, "Support-vector networks.," *Mach Learn*, vol. 20, no. 3, pp. 273–297, 1995.
- [133] P. Pradhapan, M. Swaninathan, H. K. S. V. Mohan, and N. Sriraam, "Identification of apnea during respiratory monitoring using support vector machine classifier: A pilot study.," *J Clin Monit Comput*, vol. 27, pp. 179–185, Apr 2013.
- [134] A. Tenev, S. Markovska-Simoska, L. Kocarev, J. Pop-Jordanov, A. Muller, and G. Candrian, "Machine learning approach for classification of ADHD adults.," *Int J Psychophysiol*, vol. 93, pp. 162–166, Jul 2014.
- [135] P. Qiu, X. Cai, W. Ding, Q. Zhang, E. D. Norris, and J. R. Greene, "HCV genotyping using statistical classification approach.," *J Biomed Sci*, vol. 16:62, 2009.
- [136] B. E. Pennock, "Rib cage and abdominal piezoelectric film belts to measure ventilatory airflow.," *J Clin Monit*, vol. 6, pp. 276–283, Oct 1990.
- [137] K. Dingli, E. L. Coleman, M. Vennelle, S. P. Finch, P. K. Wraith, T. W. Mackay, and N. J. Douglas, "Evaluation of a portable device for diagnosing the sleep apnoea/hypopnoea syndrome.," *Eur Respir J*, vol. 21, pp. 253–259, Feb 2003.
- [138] H. Gollee and S. Mann, "Measurement of respiratory activity during abdominal muscle stimulation.," *In: Proceedings of 8th Automed Workshop*, 2009.
- [139] D. E. Weese-Mayer, M. J. Corwin, M. R. Peucker, J. M. D. Fiore, D. R. Hufford, L. R. Tinsley, M. R. Neuman, R. J. Martin, L. J. Brooks, S. L. D. Ward, G. Lister, and M. Willinger, "Comparison of apnea identified by respiratory inductance plethysmography with that detected by end-tidal Co2 or thermistor. The CHIME Study Group.," *Am J Respir Crit Care Med*, vol. 162, pp. 471–480, Aug 2000.
- [140] R. Farr, J. M. Montserrat, M. Rotger, E. Ballester, and D. Navajas, "Accuracy of thermistors and thermocouples as flow-measuring devices for detecting hypopnoeas.," *Eur Respir J*, vol. 11, pp. 179–182, Jan 1998.
- [141] S. J. Preece, J. Y. Goulermas, L. P. J. Kenney, and D. Howard, "A comparison of feature extraction methods for the classification of dynamic activities from accelerometer data.," *IEEE Trans Biomed Eng*, vol. 56, pp. 871–879, Mar 2009.

- [142] H. Gollee and W. Chen, “Real-time detection of respiratory activity using an inertial measurement unit.,” in *In Proc 29th Annual International Conference of the IEEE EMBS*, pp. 2230–2233, 2007.
- [143] ADInstruments, *Front-end Signal Conditioners Owners Guide*, 2013. page 178.
- [144] G. J. Tortora and N. P. Anagnostakos, *Principles of anatomy and physiology*. New York: Harper-Collins, 1990.
- [145] N. M. Razali and Y. B. Wah, “Power comparisons of Shapiro-Wilk, Kolmogrov-Smirnov, Lilliefors and Anderson-Darling tests,” *JOSMA*, vol. 2, pp. 21–33, 2011.
- [146] J. Cohen, *Statistical Power Analysis for the Behavioral Sciences*. Routledge, 1969.
- [147] L. W. Murray and D. A. Dosser, “How significant is a significant difference? Problems with the measurement of magnitude of effect,” *J Couns Psychol*, vol. 34, pp. 68–72, 1987.
- [148] E. J. McCaughey, A. J. McLachlan, and H. Gollee, “Non-intrusive real-time breathing pattern detection and classification for automatic abdominal functional electrical stimulation.,” *Med Eng Phys*, vol. 36, pp. 1057–1061, Aug 2014.
- [149] D. G. Altman and J. M. Bland, “Diagnostic tests 1: Sensitivity and specificity.,” *BMJ*, vol. 308, p. 1552, 1994.
- [150] S. Song, Z. Zhan, Z. Long, J. Zhang, and L. Yao, “Comparative study of SVM methods combined with voxel selection for object category classification on fMRI data.,” *PLoS One*, vol. 6, no. 2, p. e17191, 2011.
- [151] G. Cawley and N. Talbot, “Preventing over-fitting during model selection via bayesian regularisation of the hyper-parameters.,” *JMLR*, vol. 8, pp. 841–861, 2007.
- [152] A. D. Troyer, M. Estenne, and W. Vincken, “Rib cage motion and muscle use in high tetraplegics.,” *Am Rev Respir Dis*, vol. 133, pp. 1115–1119, Jun 1986.
- [153] Y. Hiraizumi, E. Fujimaki, T. Hishida, T. Maruyama, and M. Takeuchi, “Regional lung perfusion and ventilation with radioisotopes in cervical cord-injured patients.,” *Clin Nucl Med*, vol. 11, pp. 352–357, May 1986.
- [154] M. Estenne and A. D. Troyer, “Relationship between respiratory muscle electromyogram and rib cage motion in tetraplegia.,” *Am Rev Respir Dis*, vol. 132, pp. 53–59, Jul 1985.
- [155] R. W. Reid, “Motor points in relation to the surface of the body.,” *J Anat*, vol. 54, pp. 271–275, Jul 1920.
- [156] S. Bell, J. Shaw-Dunn, H. Gollee, D. B. Allan, M. H. Fraser, and A. N. McLean, “Improving respiration in patients with tetraplegia by functional electrical stimulation: An anatomical perspective.,” *Clin Anat*, vol. 20, pp. 689–693, Aug 2007.

- [157] J. M. Bland and D. G. Altman, "Statistical methods for assessing agreement between two methods of clinical measurement.," *Lancet*, vol. 1, pp. 307–310, Feb 1986.
- [158] J. N. Caviness, A. Gabellini, C. S. Kneebone, P. D. Thompson, A. J. Lees, and C. D. Marsden, "Unusual focal dyskinesias: The ears, the shoulders, the back, and the abdomen.," *Mov Disord*, vol. 9, pp. 531–538, 1994.
- [159] G. Iliceto, P. D. Thompson, B. L. Day, J. C. Rothwell, A. J. Lees, and C. D. Marsden, "Diaphragmatic flutter, the moving umbilicus syndrome, and "belly dancer's" dyskinesia.," *Mov Disord*, vol. 5, no. 1, pp. 15–22, 1990.
- [160] G. Linazasoro, N. V. Blercom, A. Lasa, J. M. Fernandez, and I. Aranzbal, "Etiological and therapeutical observations in a case of belly dancer's dyskinesia.," *Mov Disord*, vol. 20, pp. 251–253, Feb 2005.
- [161] M. Hallett, A. Albanese, D. Dressler, K. R. Segal, D. M. Simpson, D. Truong, and J. Jankovic, "Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders.," *Toxicon*, vol. 67, pp. 94–114, Jun 2013.
- [162] N. G. Lee, J. H. You, H. D. Park, H. S. Myoung, S. E. Lee, J. H. Hwang, H. S. Kim, S. S. Kim, and K. J. Lee, "The validity and reliability of the motor point detection system: A preliminary investigation of motor points of the triceps surae muscles.," *Arch Phys Med Rehabil*, vol. 90, pp. 348–353, Feb 2009.
- [163] G. Alon, S. A. McCombe, S. Koutsantonis, L. J. Stumphauzer, K. C. Burgwin, M. M. Parent, and R. A. Bosworth, "Comparison of the effects of electrical stimulation and exercise on abdominal musculature.," *J Orthop Sports Phys Ther*, vol. 8, no. 12, pp. 567–573, 1987.
- [164] J. P. Porcari, J. Miller, K. Cornwell, C. Foster, M. Gibson, K. McLean, and T. Kernozek, "The effects of neuromuscular electrical stimulation training on abdominal strength, endurance, and selected anthropometric measures.," *J Sports Sci Med*, vol. 4, pp. 66–75, Mar 2005.
- [165] M. O. Meade, G. H. Guyatt, R. J. Cook, R. Groll, J. R. Kachura, M. Wigg, D. J. Cook, A. S. Slutsky, and T. E. Stewart, "Agreement between alternative classifications of acute respiratory distress syndrome.," *Am J Respir Crit Care Med*, vol. 163, pp. 490–493, Feb 2001.
- [166] T. D. Girard and E. W. Ely, "Protocol-driven ventilator weaning: Reviewing the evidence.," *Clin Chest Med*, vol. 29, pp. 241–252, Jun 2008.
- [167] A. I. R. Kottink, H. J. Hermens, A. V. Nene, M. J. Tenniglo, C. G. Groothuis-Oudshoorn, and M. J. IJzerman, "Therapeutic effect of an implantable peroneal nerve stimulator in subjects with chronic stroke and footdrop: A randomized controlled trial.," *Phys Ther*, vol. 88, pp. 437–448, Apr 2008.

- [168] L. D. Plank, D. N. Monk, R. Gupta, G. Franch-Arcas, J. Pang, and G. L. Hill, "Body composition studies in intensive care patients: Comparison of methods of measuring total body water.," *Asia Pacific J Clin Nutr*, vol. 4, pp. 125–128, 1995.
- [169] S. K. Shade, "Use of transcutaneous electrical nerve stimulation for a patient with a cardiac pacemaker. A case report.," *Phys Ther*, vol. 65, pp. 206–208, Feb 1985.
- [170] J. Marin, J. Nixon, and C. Gorecki, "A systematic review of risk factors for the development and recurrence of pressure ulcers in people with spinal cord injuries.," *Spinal Cord*, vol. 51, pp. 522–527, Jul 2013.
- [171] N. J. Harper, R. Greer, and D. Conway, "Neuromuscular monitoring in intensive care patients: Milliamperage requirements for supramaximal stimulation.," *Br J Anaesth*, vol. 87, pp. 625–627, Oct 2001.
- [172] H. Kern, U. Carraro, N. Adami, C. Hofer, S. Loeffler, M. Vogelauer, W. Mayr, R. Rupp, and S. Zampieri, "One year of home-based daily FES in complete lower motor neuron paraplegia: Recovery of tetanic contractility drives the structural improvements of denervated muscle.," *Neurol Res*, vol. 32, pp. 5–12, Feb 2010.
- [173] M. R. Al-Mulla, F. Sepulveda, and M. Colley, "A review of non-invasive techniques to detect and predict localised muscle fatigue.," *Sensors (Basel)*, vol. 11, no. 4, pp. 3545–3594, 2011.
- [174] N. A. Maffiuletti, M. Roig, E. Karatzanos, and S. Nanas, "Neuromuscular electrical stimulation for preventing skeletal-muscle weakness and wasting in critically ill patients: A systematic review.," *BMC Med*, vol. 11:137, 2013.

Part I

Appendices

Appendix A

Classification of Respiratory Activity

A list of the features used with the classification algorithm in Chapter 4 that were found to have a statistically significantly different median for quiet breathing and coughing, and stimulated and unstimulated breaths, is presented here. The quiet breath and cough sensitivities achieved using the classification algorithm described in Chapter 4 with different kernels and training methods are presented here. The classification accuracies that could be achieved when classifying only stimulated or unstimulated breaths are also given.

Table A.1: Features that were found to have a statistically significantly different median for quiet breathing and coughing, for all 10 participants, using the signal from a spirometer and respiratory effort belts positioned around the chest and abdomen. Statistical significance was determined using a Wilcoxon signed-rank test.

Sensor	Statistically significant Features
Spirometer	Length
	Sum
	Minimum value
	Maximum value
	Number of peaks
	Mean
	Mean magnitude (power spectral density) of Fast Fourier Transform (FFT)
	Sum of magnitude (power spectral density) of FFT
	Maximum magnitude (power spectral density) of FFT
	Minimum magnitude (power spectral density) of FFT
	Sum of magnitude (power spectral density) of FFT, divided by signal length
	Index of minimum value
	Mean gradient
	Minimum gradient
	Maximum gradient
	Sum of gradient
	Cross correlation with a quiet breath
	Cross correlation with a cough
	Mean of autocorrelation
	Maximum value of autocorrelation
	Minimum value of autocorrelation
Chest belt	Length
	Sum
	Minimum value
	Maximum value
	Number of peaks
	Mean
	Mean magnitude (power spectral density) of Fast Fourier Transform (FFT)
	Sum of magnitude (power spectral density) of FFT
	Maximum magnitude (power spectral density) of FFT
	Minimum magnitude (power spectral density) of FFT
	Sum of magnitude (power spectral density) of FFT, divided by signal length
	Mean gradient
	Minimum gradient
	Maximum gradient
	Sum of gradient
	Cross correlation with a quiet breath
	Maximum value of autocorrelation
	Minimum value of autocorrelation

Abdominal belt	Length
	Minimum value
	Maximum value
	Mean
	Mean magnitude (power spectral density) of Fast Fourier Transform (FFT)
	Minimum magnitude (power spectral density) of FFT
	Sum of magnitude (power spectral density) of FFT, divided by signal length
	Mean gradient
	Minimum gradient
	Maximum gradient
	Sum of gradient
	Cross correlation with a quiet breath
	Maximum value of autocorrelation

Table A.2: Features that were found to have a statistically significantly different median for stimulated and unstimulated breaths, for all 10 participants, using the signal from a spirometer and respiratory effort belts positioned around the chest and abdomen. Statistical significance was determined using a Wilcoxon signed-rank test.

Sensor	Statistically significant Features
Spirometer	Sum
	Minimum value
	Number of peaks
	Mean
	Mean magnitude (power spectral density) of Fast Fourier Transform (FFT)
	Sum of magnitude (power spectral density) of FFT
	Maximum magnitude (power spectral density) of FFT
	Sum of gradient
	Mean of autocorrelation
Chest belt	Minimum gradient
Abdominal belt	Index of minimum value
	Minimum gradient
	Sum of gradient

Table A.3: Mean percentage quiet breath (q) and cough (c) sensitivity (Se) (\pm standard deviation) achieved using the signals from the respiratory effort belts placed around the abdomen (abdo) and the chest, a combination of respiratory effort belt signals and the signal from a spirometer (spiro). The SVM was trained for each participant using the data collected during session one (*Train1*). Classification was performed on the data collected during session two using: a linear kernel with a boxconstraint value of 0.1, a linear kernel with an optimised (opti) box constraint value for each participant, a RBF kernel with a boxconstraint value of 1 and an a RBF kernel with an optimised boxconstraint value for each participant. * indicates statistically significantly different from spirometer when using the same training data and † indicates statistically significantly different from results achieved using a linear kernel and box constraint of 0.1.

Sensor	Linear & 0.1		Linear & opti		RBF & 1		RBF & opti	
	Se^c (%)	Se^q (%)	Se^c (%)	Se^q (%)	Se^c (%)	Se^q (%)	Se^c (%)	Se^q (%)
Spiro	93.9 \pm 9.2	98.2 \pm 2.2	97.8 \pm 2.7	97.0 \pm 3.4	96.9 \pm 5.6	91.5 † \pm 5.9	96.9 \pm 5.6	92.3 † \pm 5.9
Chest Belt	96.6 \pm 5.8	90.6* \pm 13.3	96.9 \pm 5.9	91.2 \pm 13.4	96.8 \pm 11.8	74.5* † \pm 16.9	96.1 \pm 8.2	80.2 † \pm 16.0
Both Belts	93.8 \pm 9.5	84.4* \pm 15.1	95.4 \pm 7.5	86.7 \pm 14.0	- -	- -	- -	- -
Abdo Belt	79.3* \pm 14.9	88.9* \pm 7.4	84.2* \pm 12.1	89.3* \pm 9.0	58.1* \pm 27.7	91.8 \pm 7.4	86.6* † \pm 9.7	75.7* † \pm 14.2

Table A.4: Mean percentage quiet breath (q) and cough (c) sensitivity (Se) (\pm standard deviation) achieved using the signals from the respiratory effort belts placed around the abdomen (abdo) and the chest, a combination of respiratory effort belt signals and the signal from a spirometer (spiro). The SVM was trained for each participant using the data collected during session two (*Train2*). Classification was performed on the data collected during session one using: a linear kernel with a boxconstraint value of 0.1, a linear kernel with an optimised (opti) box constraint value for each participant, a RBF kernel with a boxconstraint value of one and an a RBF kernel with an optimised boxconstraint value for each participant. * indicates statistically significantly different from spirometer when using the same training data and † indicates statistically significantly different from results achieved using a linear kernel and box constraint of 0.1.

Sensor	Linear & 0.1		Linear & opti		RBF & 1		RBF & opti	
	Se^c (%)	Se^q (%)	Se^c (%)	Se^q (%)	Se^c (%)	Se^q (%)	Se^c (%)	Se^q (%)
Spiro	84.5 ± 16.4	99.0 ± 1.2	88.7 ± 13.8	99.1 ± 1.1	80.9 ± 21.3	93.0 † ± 5.4	87.4 ± 19.4	90.5 † ± 6.5
Chest Belt	82.5 ± 14.7	97.5 ± 4.2	86.0 ± 12.6	97.3* ± 4.2	84.6 ± 16.9	88.6 † ± 5.6	85.9 ± 13.6	91.7 ± 4.0
Both Belts	74.5 ± 15.5	94.2* ± 6.7	78.6 † ± 14.2	94.1* ± 6.5	- -	- -	- -	- -
Abdo Belt	76.2 ± 12.7	90.9* ± 7.8	78.3 † ± 13.1	91.8* ± 7.7	61.8* ± 32.8	85.2 ± 12.0	74.7 ± 20.3	80.8 † ± 13.0

Table A.5: Mean percentage cough (c) and quiet breath (q) sensitivity (Se) (\pm standard deviation) of stimulated (stim) and unstimulated (unstim) breaths using the signals from respiratory effort belts placed around the abdomen (abdo) and the chest, a combination of these signals, and the signal from a spirometer (spiro). The SVM was trained for each participant using the data collected during session one (*Train1*). Classification was performed on the data collected during session two using a linear kernel and a boxconstraint value of 0.1.

Sensor	Stim Se^c (%)	Unstim Se^c (%)	Stim Se^q (%)	Unstim Se^q (%)
Spiro	93.4 ± 9.9	94.3 ± 8.9	97.7 ± 2.8	98.7 ± 1.8
Chest Belt Belt	96.5 ± 6.8	97.1 ± 6.2	87.6 ± 19.1	94.3 ± 6.5
Both Belts Belts	95.0 ± 9.7	94.3 ± 10.2	80.7 ± 22.5	90.2 ± 10.0
Abdo Belt	79.1 ± 18.1	79.8 ± 15.7	87.3 ± 9.1	91.6 ± 8.0

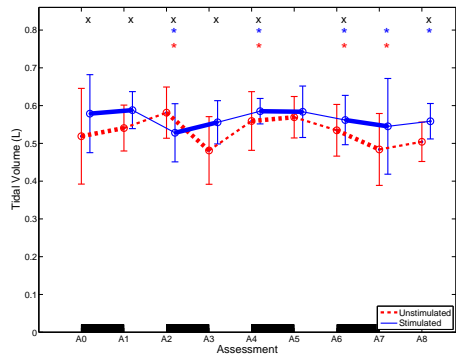
Table A.6: Mean percentage cough (c) and quiet breath (q) sensitivity (Se) (\pm standard deviation) of stimulated (stim) and unstimulated (unstim) breaths using the signals from respiratory effort belts placed around the abdomen (abdo) and the chest, a combination of these signals, and the signal from a spirometer (spiro). The SVM was trained for each participant using the data collected during session two (*Train2*). Classification was performed on the data collected during session one using a linear kernel and a boxconstraint value of 0.1.

Sensor	Stim Se^c (%)	Unstim Se^c (%)	Stim Se^q (%)	Unstim Se^q (%)
Spiro	85.8 ± 18.1	83.6 ± 17.2	99.3 ± 0.8	98.5 ± 1.7
Chest Belt	83.3 ± 19.6	82.0 ± 13.0	97.4 ± 5.0	97.3 ± 5.3
Both Belts	77.3 ± 19.5	74.6 ± 14.7	93.4 ± 7.9	95.3 ± 6.1
Abdo Belt	74.2 ± 20.2	79.5 ± 8.6	89.9 ± 8.0	92.3 ± 9.0

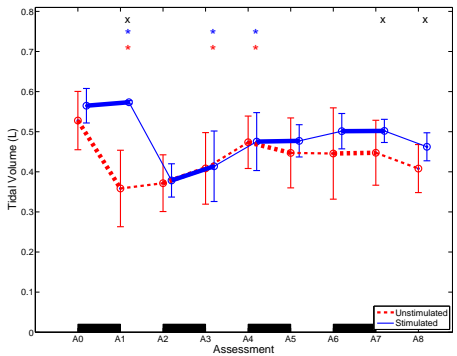
Appendix B

Ventilator Weaning Study Data

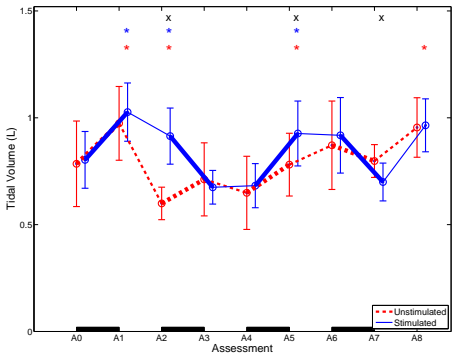
The Tidal Volume (V_T) and Vital Capacity (V_C) results of Participants 2 to 4 and 6 to 10 from the clinical study presented in Chapter 6 are given here.



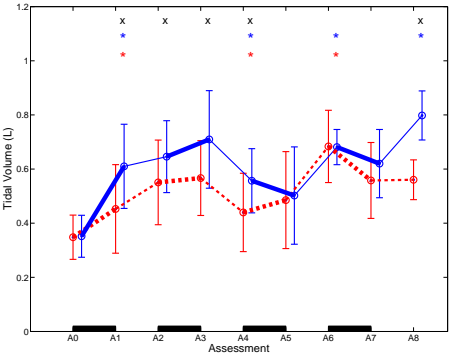
(a) Participant 2.



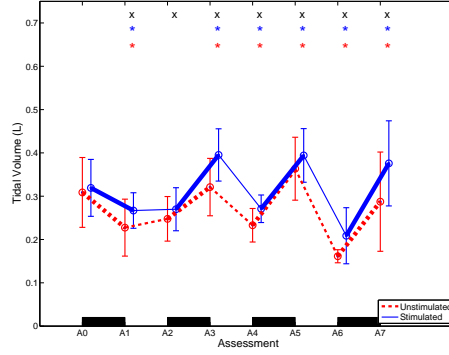
(b) Participant 3.



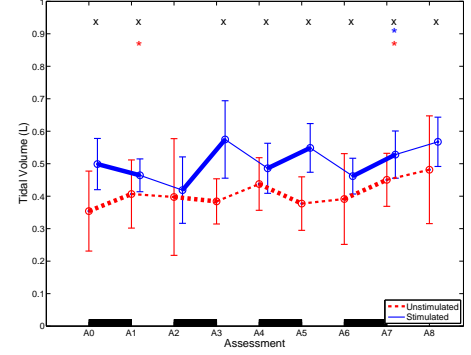
(c) Participant 4.



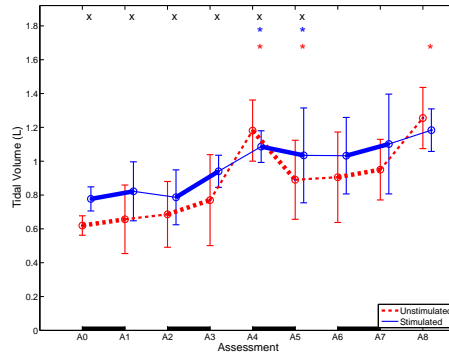
(d) Participant 6.



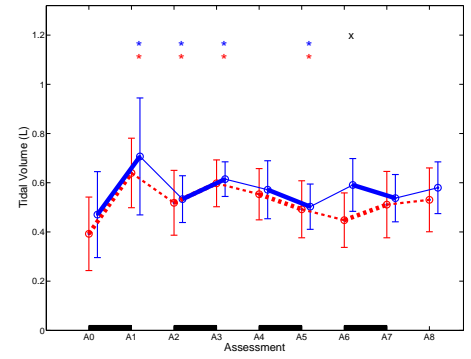
(e) Participant 7.



(f) Participant 8.

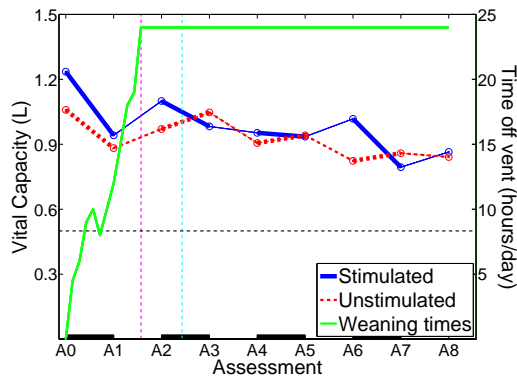


(g) Participant 9.

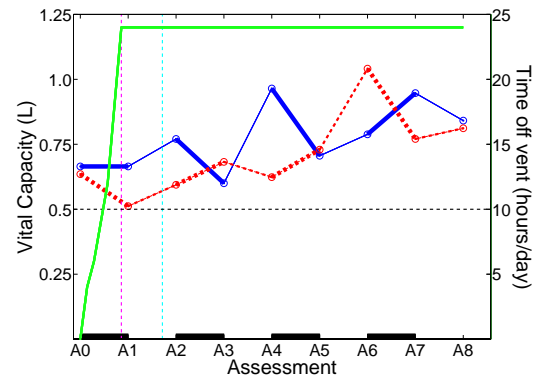


(h) Participant 10.

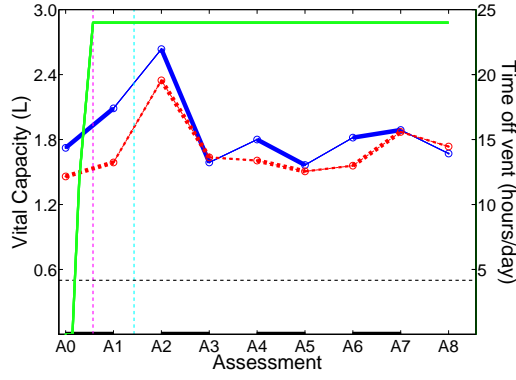
Figure B.1: Tidal Volume (V_T) \pm standard deviation of Participants 2 to 4 and 6 to 10, recorded at nine weekly assessment sessions, where a blue line represents stimulated, and a red line unstimulated, breaths. The solid black line along bottom of plot represents one week of AFES training and no line indicates one week with no training. Black x indicates stimulated V_T was statistically significantly different to unstimulated V_T , blue * indicates that stimulated V_T was statistically significantly different to stimulated V_T recorded at previous assessment and red * indicates that unstimulated V_T was statistically significantly different to unstimulated V_T recorded at previous assessment.



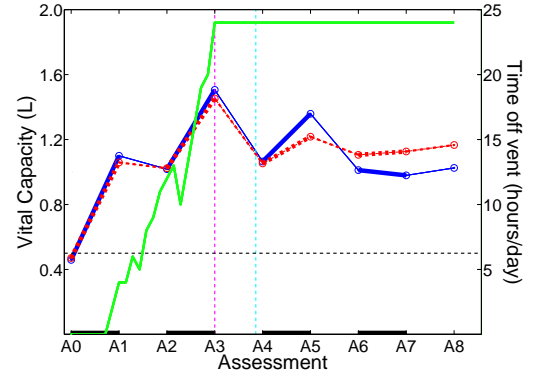
(a) Participant 2.



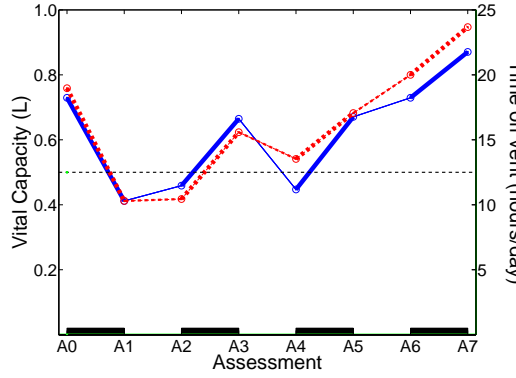
(b) Participant 3.



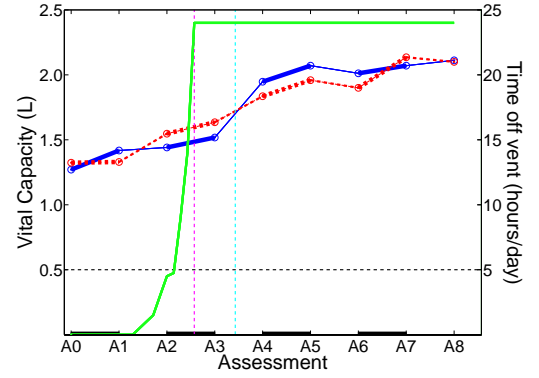
(c) Participant 4.



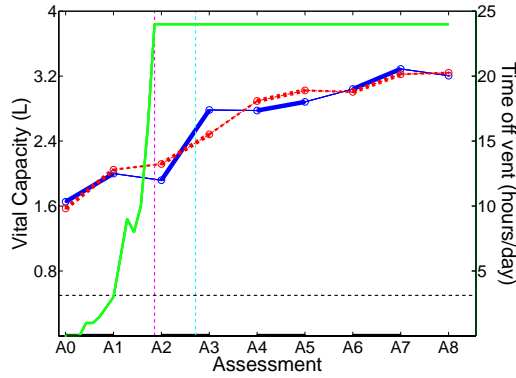
(d) Participant 6.



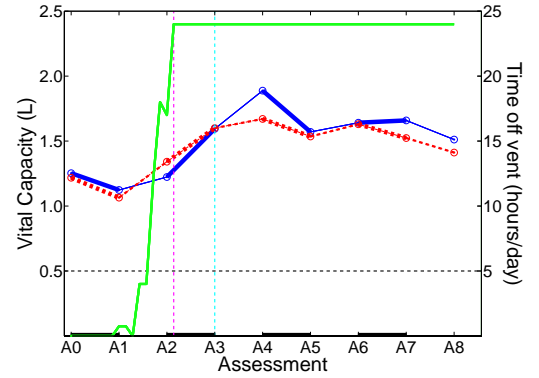
(e) Participant 7.



(f) Participant 8.



(g) Participant 9.



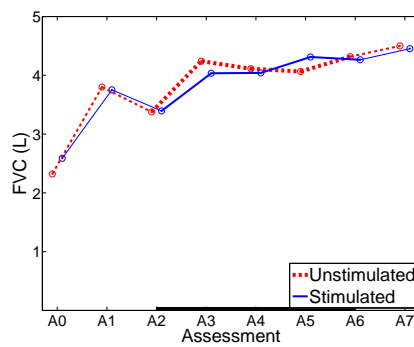
(h) Participant 10.

Figure B.2: Vital Capacity (V_C) of Participants 2 to 4 and 6 to 10, recorded at nine weekly assessment sessions, where a blue line represents stimulated, and a red line unstimulated, breaths. The solid black line along bottom of plot represents one week of AFES training and no line indicates one week with no training. Green line represents time spent breathing without ventilator support per day, while broken black line represent a V_C of 500 mL, the V_C at which participants were expected to wean based on clinical experience. The dashed magenta line represents the time point at which the participant achieved 24 hours of ventilator free breathing, while the dashed cyan line represents the time point at which the participant achieved seven days of ventilator free breathing.

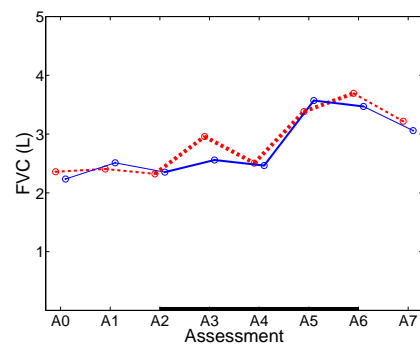
Appendix C

Cough Assist Study Data

The Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF) and Forced Exhaled Volume in one second (FEV_1) of Participants 3 and 4 from the study presented in Chapter 7 are given here, along with the effect size of these measures.



(a) Participant 3.



(b) Participant 4.

Figure C.1: Forced Vital Capacity (FVC) of Participants 3 and 4 recorded at eight fortnightly assessment sessions, where a blue line represents stimulated, and a red line unstimulated, breaths. Solid black line along the bottom of the plot represents the eight week period of AFES training and no line indicates no training.

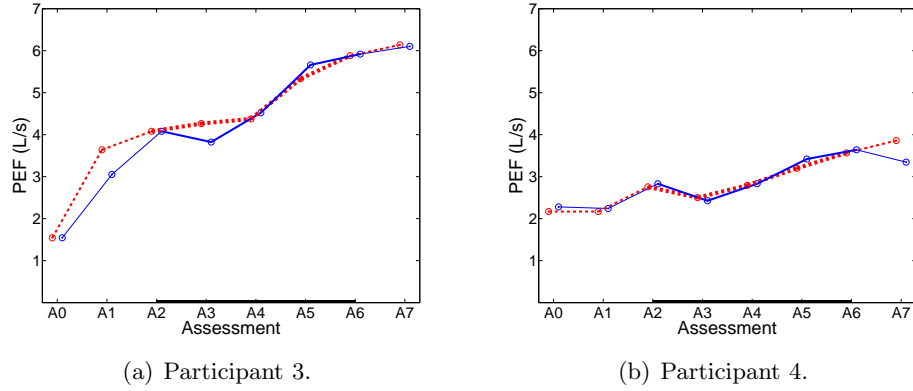


Figure C.2: Peak Expiratory Flow (PEF) of Participants 3 and 4 recorded at eight fortnightly assessment sessions, where a blue line represents stimulated, and a red line unstimulated, breaths. Solid black line along the bottom of the plot represents the eight week period of AFES training and no line indicates no training.

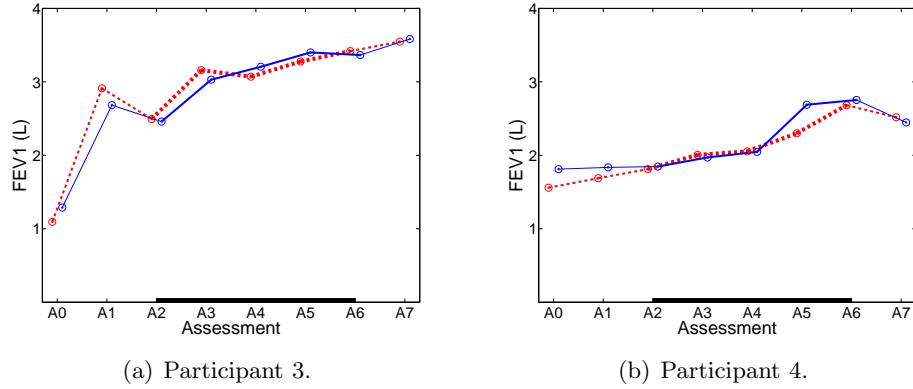


Figure C.3: Forced exhaled volume in one second (FEV_1) of Participants 3 and 4 recorded at eight fortnightly assessment sessions, where a blue line represents stimulated, and a red line unstimulated, breaths. Solid black line along the bottom of the plot represents the eight week period of AFES training and no line indicates no training.

Table C.1: Effect sizes (ES) and lower (LI) and higher (HI) confidence intervals for changes in stimulated (stim) and unstimulated (unstim) weight corrected Forced Vital Capacity (FVC/kg), weight corrected Peak Expiratory Flow (PEF/kg) and weight corrected Forced Exhaled Volume in one second (FEV_1 /kg) across the 14 week study duration, four week control period and eight week intervention period.

Measure	Stim	Study			Control			Training		
		LI	ES	HI	LI	ES	HI	LI	ES	HI
FVC/kg	Stim	0.97	1.90	2.83	0.76	1.67	2.58	0.29	1.15	2.01
	Unstim	0.75	1.65	2.56	0.26	1.12	1.98	0.29	1.16	2.02
PEF/kg	Stim	0.72	1.62	2.52	0.59	1.47	2.36	-0.05	0.78	1.62
	Unstim	0.86	1.78	2.69	0.68	1.58	2.48	-0.06	0.77	1.61
FEV_1 /kg	Stim	0.36	1.22	2.09	0.07	0.92	1.76	0.05	0.89	1.73
	Unstim	0.80	1.71	2.63	0.84	1.76	2.68	0.11	0.96	1.80