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ABDOMINAL STIMULATION FOR VENTILATION IN TETRAPLEGIA

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Abstract

The respiratory system is highly compromised after a tetraplegic Spinal Cord Injury (SCI) due to paralysis of the major breathing muscles. As a result Mechanical Ventilation (MV) is often required and respiratory complications are a major cause of rehospitilisation, morbidity, and early mortality. Functional Electrical Stimulation (FES) applied acutely to the abdominal wall muscles in synchrony with a patient's volitional exhalation has been shown to improve breathing volumes and the ability to cough in spontaneously breathing tetraplegic patients. It has also been used acutely to improve breathing volumes in otherwise mechanically ventilated patients. The effect of using Abdominal Functional Electrical Stimulation (AFES) chronically on AFES-assisted and unassisted respiratory function is currently unknown. To support clinical adoption of AFES practical systems are required. Systems that synchronise AFES with exhalation automatically have been developed but they have relied on invasive respiratory sensors.

In the first clinical study of this thesis twelve tetraplegic patients who could breathe spontaneously completed a three week AFES training programme in addition to a one week pre-training control period and a three week post-training follow up period. The results showed a significant increase in AFES-assisted Forced Vital Capacity (FVC), and unassisted FVC, Peak Expiratory Flow (PEF), and Cough Peak Flow (CPF) throughout the training period. AFES-assisted PEF and CPF tended to increase over the same period, but the increase was not significant. The difference between unassisted and AFES-assisted measures did not change. Overall, there were limited changes in the outcome measures during the control and follow up periods, which suggests that the changes in outcome measures observed during the training period were a response to training.

In the second clinical study daily sessions of AFES-breathing were combined with the standard of care during the process of weaning a single tetraplegic patient from MV. The results showed that the approach was feasible: AFES acutely increased the duration of ventilator free breathing at the start of the weaning process and daily ventilator free breathing improved considerably during two

four-week long periods of daily AFES-assisted breathing.

In the final study breathing data was recorded from ten healthy volunteers using a spirometer (the current standard), a nasal thermocouple, and piezoelectric belts wrapped around the chest and abdomen. An algorithm was written for each of the sensors so that they could be used to trigger stimulation during quiet breathing. The thermocouple system, followed by the chest belt system, were shown to be the most suitable replacement sensors for the spirometer.

The results of this thesis suggest three different applications of AFES in tetraplegia: a neurorehabilitation device that can be used to improve unassisted respiratory function in spontaneously breathing tetraplegics; a neuroprosthesis device that could be used to assist spontaneously breathing tetraplegics in times of respiratory distress, e.g. during recovery from respiratory infection; and as a method of weaning tetraplegic patients from MV. The realisation of these applications will be assisted by the non-invasive respiratory sensor algorithms developed in this thesis. Collectively these results have demonstrated the feasibility of several new areas of future research, which could ultimately be of great benefit to the health of patients with tetraplegia.

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Thesis Outline

Chapter 1 The epidemiology and consequences of tetraplegia are described with a particular focus on respiratory problems in this patient group. The current standard of respiratory care is presented and the unmet medical needs are identified. AFES is put forward as a potential solution to the unmet needs, a summary of the current knowledge of AFES is given and the open questions addressed in this thesis are formulated.

Chapter 2 The healthy respiratory system is explained and compared with the respiratory system in tetraplegia. This is followed by a detailed description of AFES technology and its alternatives. In conclusion there is a critical review of the literature related to the effects of AFES on the respiratory system.

Chapter 3 The subjects and general methods employed to investigate a three week AFES training programme and its effects on unassisted and AFES-assisted respiratory function are detailed.

Chapter 4 The results of three weeks of AFES training on unassisted and AFES-assisted standard clinical tests are presented and discussed.

Chapter 5 The results of three weeks of AFES training on unassisted and AFES-assisted coughing are presented and discussed.

Chapter 6 The results of three weeks of AFES training on unassisted and AFES-assisted quiet breathing are presented and discussed.

Chapter 7 The use of AFES in combination with standard of care to assist the process of weaning a tetraplegic patient from MV is described. The methods and results are presented and the feasibility of using AFES for ventilator weaning is discussed.

Chapter 8 The design and evaluation of three new sensor and algorithm systems for the purpose of providing stimulation automatically during quiet

breathing are presented and discussed.

Chapter 9 The findings of this thesis and the role of AFES in the clinical setting are discussed. After this discussion the conclusions of this thesis are drawn.

Chapter 10 The areas of interest for future work are discussed.

Contributions

- This thesis delineated the use of AFES to improve respiratory function into three clinical applications: as a neuromuscular training device for respiratory rehabilitation, as a respiratory neuroprosthesis that could be used in times of respiratory distress and as a tool to assist in the process of weaning patients from MV.

- This thesis was the first to examine the effects of a passive training programme on respiratory function in tetraplegia. Previous training modalities have either required active participation by the patient or have stimulated more than one group of respiratory muscles. In contrast, the training programme presented in this thesis was easy and quick to apply and allowed patients to complete other activities at the same time of training, for example hand rehabilitation. These advantages are expected to be useful in a busy clinical setting.

- This thesis was the first to show that three weeks of passive AFES training can improve unassisted and AFES-assisted respiratory function. The results of this thesis suggest that AFES-assisted respiratory function changed in response to a change in unassisted respiratory function rather than a change in the contractile properties of the abdominal muscles. Several novel hypothesis were proposed to explain these results which can be used to help design future passive AFES training programmes.

- The temporal response of ventilatory parameters during AFES-assisted breathing was examined for the first time. Importantly this showed that in most tetraplegic patients End Tidal Carbon Dioxide (ET_{CO_2}) did not increase during AFES-assisted breathing. This result, coupled with the finding that AFES-assisted breathing increased blood oxygenation during AFES-assisted MV weaning sessions, suggest that AFES-assisted breathing is metabolically efficient.

- A novel weaning protocol to use AFES in combination with standard of care to assist in the process of weaning tetraplegic patients from ventilation was developed. The feasibility of this protocol was tested in a case study which provided preliminary evidence on the efficacy of AFES-assisted weaning.

- Stimulation algorithms, one of which used the output of a nasal / oral thermocouple the other the output of a piezoelectric belt wrapped around the chest, were developed and evaluated quantitatively. These algorithms can be used for applying stimulation automatically both during AFES neuromuscular training and also during AFES-assisted weaning sessions respectively.

Publications

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Abbreviations

AFES   Abdominal Functional Electrical Stimulation

AIS   ASIA Impairment Scale

ANOVA   Analysis of Variance

ASIA   American Spinal Injuries Association

ATS   American Thoracic Society

BPM   Breaths per Minute

$Blank_E$ The proportion of the previous inhalation period that determined the length of the blanking window used to reduce the number of false exhalation detections in the peak detection and zero crossing algorithms

$Blank_I$ The proportion of the previous exhalation period that determined the length of the blanking window used to reduce the number of false inhalation detections in the peak detection and zero crossing algorithms

BR   Breathing Rate

BW_E The size of the window that was examined before the start of a potential exhalation in the peak detection and zero crossing algorithms

BW_I The size of the window that was examined before the start of a potential inhalation in the peak detection and zero crossing algorithms

CFT   Constant Frequency Train

CIT   Catchlike Inducing Frequency Train

cmH$_2$O   centimeters of water

CPF   Cough Peak Flow

ERS   European Respiratory Society

ET$_{co_2}$ End Tidal Carbon Dioxide

FES   Functional Electrical Stimulation

FEV$_1$ Forced Exhaled Volume in One second

FMS   Functional Magnetic Stimulation

FVC   Forced Vital Capacity

FRC   Functional Residual Capacity

FW_E The size of the window that was examined after the start of a potential exhalation in the peak detection and zero crossing algorithms

FW_I The size of the window that was examined after the start of a potential inhalation in the peak detection and zero crossing algorithms

GUI   Graphical User Interface

MV   Mechanical Ventilation

MEP   Maximum Expiratory Pressure

PEF   Peak Expiratory Flow

QB   Quiet Breathing

QENSIU   Queen Elizabeth National Spinal Injuries Unit

SBT   Spontaneous Breathing Trial

SCI   Spinal Cord Injury

SCS   Spinal Cord Stimulation

τ_{cdflow} The derivative of flow rate during inspiration that was used by the cough stimulation algorithm to mark the end of inhalation

τ_{cflow} The flow rate during inspiration that was used by the cough stimulation algorithm to register an attempt to cough

τ_{cstim} The duration of cough stimulation in seconds

$\mathbf{T_{I/TOT}}$ Fractional Inspiratory Time

$\mathbf{\dot{V}}$ Minute Ventilation

$\mathbf{V_I}$ Inhaled Volume

$\mathbf{V_T}$ Tidal Volume

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Chapter 1

Introduction

A Spinal Cord Injury (SCI) at the cervical region of the spine (i.e. neck vertebrae C1 to C7) results in tetraplegia. Tetraplegia is associated with a degree of paralysis which affects all four limbs and the trunk. In particular, a tetraplegic SCI can include paralysis of the main inspiratory and expiratory breathing muscles: the diaphragm, the intercostal muscles and the abdominal muscles.

Breathing muscle paralysis in tetraplegia results in several complications but the most prominent of these are atelectasis (collapse of the lung) and pneumonia (inflammation of the lung caused by bacterial or viral infection, which results in the alveoli filling with fluid). Despite improvement in respiratory health care over the last 20 years, respiratory complications remain one of the leading causes of death and morbidity for patients with tetraplegia. Thus, there is motivation to develop new approaches to improve respiratory health for this patient group.

One approach is the application of electrical stimulation to the abdominal muscles in synchrony with a patient's volitional exhalation. This technique uses electrical stimulation of the abdominal muscles for a functional purpose, and will be referred to as Abdominal Functional Electrical Stimulation (AFES) throughout this thesis. Previous research has shown that AFES can be used acutely with tetraplegic patients to improve tidal volume during resting breathing, as well as peak flow rates during coughing. The chronic effects of AFES on the respiratory system are currently unknown. Furthermore, existing technology only supports the use of AFES in the research setting. This thesis seeks to investigate these open questions and to explore the potential practical applications of AFES as a method to improve the respiratory function of patients with tetraplegia.

In this chapter an overview of tetraplegia and its associated respiratory complications will be given. This will be followed by a summary of AFES and its present applications and limitations. This chapter concludes with the formulation

of the open questions which are addressed in this thesis.

1.1 Tetraplegia

SCI causes a disruption in communication between the brain and the rest of the body. A tetraplegic SCI occurs when the injury is at the cervical level of the spine and is associated with paralysis and a loss of sensation which affects all four limbs and the trunk.

1.1.1 Etiology, Incidence and Prevalence

The majority of SCIs result from traumatic injuries including motor vehicle accidents, falls, violence and sports and recreation. The incidence of each of these causes varies between countries; Table 1.1 shows an approximate range of rates for each cause [107, 129]. SCI may also result from non-traumatic causes including, but not limited to, multiple sclerosis, spina bifida and cerebral palsy [107].

Table 1.1: Etiology of traumatic SCI

Cause of Injury	Incidence (%)
Motor vehicle accidents	35 - 50
Falls	17 - 20
Violence	5 - 29
Sports and recreation	7 - 25

Approximately one third of SCI will result in tetraplegia; it affects millions of patients across the world and there are thousands of new cases every year. A recent literature review found that the average number of SCI per one million inhabitants is 755 in North America, 252 in Europe and 681 in Australia. In addition, the average number of new injuries per million inhabitants per year is estimated at 51 in North America, 19 in Europe and 17 in Australia [156].

Most SCI appear to occur in young males. It is reported that the average age at the time of SCI is 33 and that there is 3.8 times more male SCI than female SCI [107, 156].

1.1.2 Consequences of Tetraplegia

The primary consequence of tetraplegia is muscle paralysis and a loss of sensation which affects all of the parts of the body that are innervated below the level of injury. This will include paralysis of the breathing muscles for most patients, as

well as partial or complete paralysis of the trunk, arms and legs. In addition to the level of injury, the degree of impairment inflicted by tetraplegia is also related to the completeness of the transection of the spinal cord. The completeness of the injury is determined by a motor and sensory neurological examination, and graded according to the American Spinal Injuries Association (ASIA) impairment scale (AIS) [103]. This is discussed in detail in Chapter 2.

A myriad of secondary complications follow from the primary complications with respiratory complications among the most common [25, 77, 108, 151].

1.1.3 Prognosis

In the past a SCI was associated with a considerably lower life expectancy compared with able-bodied people. As a result of increasing standards of care, SCI life expectancy is increasing [151], although it remains lower than that of the able-bodied population [25]. The major factors affecting the life expectancy of tetraplegic patients are: level and completeness of injury; age at the time of injury; ventilator status (i.e. the extend to which a patient can breathe spontaneously); time from injury; and secondary complications [36, 129, 151].

Ventilator status plays a key role in life expectancy: it is the strongest predictor of survival during the first year of injury when mortality rates are greatest [36]. Respiratory complications, which are closely correlated to ventilator status, are the leading cause of mortality after the first year of injury. Strikingly, one study found that respiratory complications were the only cause of death after the first year of injury [36].

Secondary complications have a significant effect on tetraplegic patients: hospitalisation arising from secondary complications is between 1.7 and 2.4 times the rate of the able bodied population [77]. Additionally, during the acute-care period after SCI, the length of hospital stay is significantly related to the number of respiratory complications [153].

Despite the morbidity and mortality associated with SCI, most patients have a positive view of their quality of life, with the highest ratings coming from the younger age group [77, 151]. In one study, only 15% of patients reported that their quality of life was poor and less than 3% described themselves as being depressed [77].

1.1.4 Economic Cost of Spinal Cord Injury

SCI places a huge financial burden on health care providers. It is difficult to get data from the UK, but reports in the USA estimate initial hospital costs at $95,000, home modification at $8,000, and ongoing costs (excluding the costs of hospitalisation from secondary complications) at $14,000 [129]. A leading contributor to hospital costs is treatment for respiratory complications [153], with one centre in Europe estimating the cost of a single respiratory treatment at 19,000 Euros [71].

1.2 Respiratory Complications in Tetraplegia

In patients with tetraplegia, paralysis of the main breathing muscles [154], muscle atrophy [26, 51, 63, 142] and changes in the mechanical properties of the lung [48, 54, 126] severely compromise ventilation. As a result, patients suffer from dyspnea [23] and the inability to cough [154]. In severe cases, patients suffer complete diaphragmatic paralysis and are unable to sustain adequate ventilation without artificial support [32, 74]. The reduced respiratory function of tetraplegic patients has considerable implications for their health and general well-being. Respiratory complications are one of the main causes of rehospitalisation and early mortality in tetraplegia [25, 36]. Furthermore, they are a burdening source of morbidity for patients and their relatives [153].

1.2.1 Ventilation

Many patients with tetraplegia will initially require Mechanical Ventilation (MV) to support their breathing. The incidence of patients being unable to sustain independent ventilation in the initial stages of injury is highest in those with an injury between C1 and C4 (40%) but it also occurs in those with an injury between C5 and C8 (23%) [74]. Most tetraplegic subjects with a motor complete SCI will require a period of ventilation in the early stages of injury [32]. In comparison, the incidence of MV is considerably lower in those subjects with an incomplete injury [32].

For those patients who require MV only some of them will wean from the ventilator. Those patients who fail to wean will mostly include subjects who have paralysis that affects the diaphragm (injuries at C5 or above) but can also include injuries in which diaphragm function is spared [32].

There are several ventilator strategies that can be used in the process of weaning a patient from MV. These include progressive ventilator free breathing and intermittant mandatory ventilation [119]. While existing ventilator strategies differ in their implementation, they are similar in that they all aim to gradually reduce the work of breathing performed by the ventilator so that the patient's respiratory system can become reconditioned to breathing independently [47]. Unfortunately, however, there are limited treatments that can be used to accelerate the process of weaning patients from MV.

Unmet Medical Need

Prolonged MV is associated with significantly increased mortality [152], significantly reduced quality of life and a significant economic cost to the health care provider. Currently, there are limited interventions that can be used to reduce weaning time and improve the probability of weaning in patients who have difficulty weaning from MV. Therefore, there is an unmet medical need for new approaches that can improve weaning outcome in patients with tetraplegia.

1.2.2 Spontaneously Breathing Tetraplegics

Those patients with less severe tetraplegic injuries have a good chance of weaning from MV, however, they will remain at high risk of developing respiratory infections and dyspnea.

Coughing

One of the major reasons that patients are susceptible to respiratory complications is because they are unable to generate an effective cough.

The lung is an organ which has the largest surface area in the body exposed to the external environment. Coughing is an important part of the lung's physical defense mechanisms which helps to remove mucus which contains bacteria and foreign particles. By failing to remove this mucus the lung is susceptible to pneumonia, atelectasis and respiratory failure [106].

In tetraplegia, the paralysis of the main expiratory muscles (the abdominal and internal intercostal muscles), and the impaired ability to inhale, limits the intra-thoracic pressure that can be generated during the compressive phase of coughing [117]. Patients are unable to produce a Cough Peak Flow (CPF) sufficient to dislodge secretions and consequently are susceptible to respiratory infections.

Tidal Volume and Dyspnea

In tetraplegic patients who are still able to breathe spontaneously, the capacity to ventilate the lung is reduced by respiratory muscle paralysis and changes in the mechanics of breathing. This may contribute to dyspnea [23], incidence of atelectasis [23, 154] and likelihood of acute respiratory failure [154].

Respiratory Management

Respiratory management in tetraplegia can be broken into two categories: prophylactic treatment and treatment after respiratory complications develop. This section will give an overview of the common techniques used. For a complete description the reader is directed toward the review by Berlley and Shem [12] and the physiotherapist text book by Bromley [22].

Prophylactic Treatment   Prophylactic treatment includes a variety of techniques such as breathing exercises, positioning and postural drainage, and coughing.

Breathing exercises can be useful in maintaining lung expansion in all areas. Their aim is to increase respiratory reserve so that patients can deal more effectively with respiratory problems.

Constant repositioning while a patient is lying in bed promotes mobilisation of mucus and sputum within the lungs. Alternatively, if a patient is neurologically stable, then postural drainage is appropriate. This uses the effect of gravity to move secretions from the peripheral airways.

As discussed, the ability to cough in tetraplegia is highly compromised. To improve the ability to cough the patient can either be assisted by a physiotherapist or can use techniques to self-assist. The goal of the physiotherapist when assisting with a cough is to imitate the function of the paralysed abdominal muscles.

Treatment During Respiratory Complications   When respiratory complications develop the following treatment options may be appropriate.

- Oxygen therapy is used when the partial pressure of oxygen in the blood is low. It involves giving the patient supplemental oxygen via a face mask or tracheostomy.

- Humidification of thick mucus is accomplished using a saline nebulizer, this thins and loosens the mucus and makes it easier to clear.

- Drugs, such as antibiotics, steroids or bronchodilators can also be used to relieve the symptoms of respiratory complications.

- Mechanical insufflation-exsufflation devices are used to clear retained secretions and work by slowly applying a positive pressure to the airways which is followed by a rapid switch to negative pressure. The shift in pressure produces a large peak expiratory flow from the airways thus simulating the actions of a cough.

- Suctioning is used to clear mucus build up in the upper airways by inserting a small diameter catheter either through the mouth or the tracheostomy opening.

- Short term mechanical ventilation using either continuous positive airway pressure or intermittent positive pressure breathing can be used to open the smaller airways and prevent alveolar collapse.

Unmet Medical Need

Despite the variety of methods now available to maintain respiratory hygiene and to treat respiratory complications when they occur, respiratory complications remain one of the leading causes of death and a major source of morbidity in spontaneously breathing tetraplegics. The lack of an effective cough is a major contributor to respiratory complications. Thus, there is a need to develop new methods for enhancing cough in tetraplegia. Dyspnea also affects the quality of life of many tetraplegic patients. Therefore, there is also a need for new methods of improving tidal volume in tetraplegic patients.

1.3 Abdominal Functional Electrical Stimulation

An appealing approach to the unmet medical needs described is the restoration of function to the respiratory muscles that were paralysed by the injury. This can be achieved by using neuromuscular electrical stimulation to induce an action potential in the motor nerve that supplies the muscle [130].

There are several types of neuromuscular stimulation. These include, transcutaneous Functional Electrical Stimulation (FES), percutaneous FES, implanted FES, Spinal Cord Stimulation (SCS) and Functional Magnetic Stimulation (FMS). Each of these paradigms have been shown to be useful for improving one or more aspects of respiratory function in tetraplegia. A full description of these

paradigms and their clinical benefit is given in Chapter 2. AFES is the method of choice in this thesis for the following relative advantages: it is easy to apply compared with percutaneous FES; the equipment required is small and portable compared with FMS; and it does not require surgery, unlike implanted FES or SCS.

1.3.1 Previous Work

AFES was used initially in tetraplegia as a cough respiratory neuro-prosthesis [93]. This was achieved by attempting to mimic the normal physiological recruitment of the abdominal muscles during cough. Specifically, the onset of AFES was synchronised with the patients closing their glottis and AFES was applied continuously throughout exhalation. Using this method, it has been shown that CPF is significantly greater during AFES-assisted cough compared with unassisted cough [24]. Since the efficacy of a cough is mainly dependent on the CPF generated [146], it is assumed that chronic use of an AFES-assisted cough device would reduce respiratory complications in tetraplegia.

Previous work has also shown that AFES can be used as a respiratory neuro-prosthesis to improve tidal volume during quiet breathing by applying stimulation in synchrony with a patient's volitional exhalation. This technique has been shown to be efficacious both in spontaneously breathing tetraplegic patients [57, 134], and in patients whose diaphragms were completely paralysed [78].

In addition to using AFES as a neuro-prosthesis, emerging evidence suggests AFES could also be useful for neuromuscular training to improve unassisted breathing function. Previous research has shown that interventions which include AFES, in addition to stimulation of other muscle groups [27] and breathing exercises [159], can improve unassisted standard clinical pulmonary function measures.

Most of the studies describing AFES have included a rudimentary system where stimulation is applied manually by either the researcher or the patient. While it may be feasible to trigger AFES manually in a research setting, a more practical solution would be to control the stimulation automatically. In this regard there have been several studies that have proposed solutions. A common approach is to use a sensor which measures air flow rate at the mouth (i.e. a spirometer or pneumotachograph), and combine it with an algorithm that applies stimulation at the correct point in the breathing cycle [57]. While this approach has been shown to work well, the choice of respiratory sensor poses a major drawback as it requires the patient to wear a face mask which interferes with

other activities such as eating or speaking

1.3.2 Open Questions

Previous research has demonstrated the effectiveness of using AFES acutely to improve respiratory function in tetraplegia. However, the chronic effects of AFES on the respiratory system are currently unknown. In addition, the current technology only supports the use of AFES in the research setting. This thesis aims to address these issues by answering the following open questions.

What effect does AFES neuromuscular training have on AFES-assisted breathing in tetraplegia? An important secondary complication of SCI is muscle disuse atrophy which occurs rapidly after the injury. Specifically, it has been shown that in the chronic stages of injury the thickness of the abdominal wall is reduced by up to 34% in tetraplegic patients [51]. Thus, it is plausible that by reducing the disuse atrophy of the abdominal muscles, the efficacy of AFES-assisted coughing or quiet breathing may be improved.

What effect does AFES neuromuscular training have on unassisted breathing in tetraplegia? Previous research has shown that neuromuscular training programmes that incorporate AFES improve unassisted breathing in tetraplegia. It is not known whether a training programme that uses AFES exclusively would be efficacious. An exclusive AFES training programme has two main advantages over the other programmes which use AFES in combination with other therapies: it is a passive programme (does not require patient interaction), which allows the patient to participate in other activities at the same time as training; it is quicker and easier to apply stimulation electrodes to one muscle group rather than to several groups. This is an important consideration in a busy hospital.

Can AFES be used to assist in the process of weaning tetraplegic patients from mechanical ventilation? Although AFES is effective in inducing relatively large tidal volumes in otherwise MV dependent patients, it is unlikely that AFES will be used to support extended periods of ventilator free breathing in the foreseeable future, as the pattern of muscle fibre recruitment when using FES is physiologically inefficient and causes the muscle to fatigue quickly. However, given that AFES can temporarily enhance breathing volumes, and that this thesis found that AFES neuromuscular training can increase unassisted maximum

breathing capacity in spontaneously breathing tetraplegics, AFES may provide the basis of a novel weaning protocol that could reduce the duration and improve the probability of patients weaning from MV.

Can an accurate method of triggering stimulation automatically using a non-invasive respiratory sensor be developed? A key aspect of AFES that will allow it to be adopted in the clinic is the technology that supports the clinical protocols that are designed. In order to be able to apply stimulation at the correct point in the breathing cycle it is necessary to have a measurement of the patient's respiratory activity. There are several respiratory sensors which are currently used for sleep monitoring studies that could be used in this application. While some respiratory sensors which could be used as an alternative to a spirometer have been previously investigated, no previous studies have quantified the accuracy of the designed systems properly.

1.4 Thesis Overview

Chapter 2 reviews the relevant literature. This includes a review of the effects of AFES and other types of neuro-prostheses on pulmonary function in tetraplegia; a review of the effects of muscle training, using either FES or other techniques, on the respiratory system in tetraplegia; and a review of respiratory sensors and AFES control approaches.

In Chapters 3 to 6 the first study of this thesis is presented. This study investigated the effects of a three week AFES intervention on both unassisted and AFES-assisted breathing in spontaneously breathing tetraplegics. In Chapter 3, the materials and methods of this study are presented. In Chapters 4 to 6 the effects of the intervention on Forced Vital Capacity (FVC) and Maximum Expiratory Pressure (MEP), coughing, and quiet breathing are presented respectively. Chapter 7 describes the second study of the thesis which evaluated the possibility of using AFES as a tool to assist with weaning from MV. The final study of the thesis is presented in Chapter 8. In this study a range of respiratory sensors were tested and compared to the output of a spirometer.

In Chapter 9 the findings from Chapters 3 to 8 are corroborated and discussed, and the conclusions of the thesis are drawn. Finally, areas of future work are suggested in Chapter 10.

Chapter 2

Background and Literature Review

This chapter establishes the background to, and context of, this thesis and presents the key literature relating to AFES. It includes a description of, and methods of measuring changes to, the healthy respiratory system. It also contains a detailed analysis of the effects of tetraplegia on the system. It then describes the essential attributes of FES and compares it to similar neuromuscular stimulation technologies. Once the background has been established it reviews the literature relating to AFES: both the technological approaches to its implementation and the clinical evidence supporting its use to improve the respiratory function in tetraplegia.

2.1 The Healthy Respiratory System

The primary function of the respiratory system is to facilitate the transfer of oxygen and carbon dioxide to and from the blood supply to meet the metabolic demands of the body. The three main aspects of this process are: control of the breathing muscles, ventilation of the lung and diffusion across the blood-gas barrier.

2.1.1 Control of Respiration

The control of respiration is primarily autonomous. The basic rhythm of breathing is modulated by the respiratory control centre located in the medulla and pons of the brain stem [141, 150, 158]. In addition, interneurons located within the spinal cord can contribute to the regulation of breathing [141]. The objective

of the autonomous breathing controller is to maintain blood gas levels within a normal range. It does this by monitoring the partial pressures of carbon dioxide and oxygen in the blood, via central and peripheral chemoreceptors, and adjusting the respiratory muscle output accordingly.

Although the basic rhythm of breathing is based on blood gas concentrations, ventilation is also modulated according to sensory input from stretch and irritant receptors in the lung, nose and upper airway; joint and muscle receptors; arterial baroreceptors and the sensation of pain or temperature. Breathing pattern may also be modulated by the central cortex in response to emotional events or through voluntary effort [141, 150].

2.1.2 Ventilation

The output from the respiratory control centre signals and coordinates the actions of the breathing muscles. The role of the breathing muscles is to expand (inhalation) or compress (exhalation) the lung. When the lung changes volume a pressure differential is created between the inside of the lung and the outside atmosphere. This difference in pressure is the driving force that causes air to be inhaled or exhaled from the lung.

Ventilation consists of two phases: inhalation and exhalation. Ventilation is mainly achieved using the main inspiratory muscles which are the diaphragm and the external intercostal muscles. These muscles are supported when necessary by the accessory inspiratory muscles, which include the scalene and sternocleidomastoids and by expiratory muscles which include the the internal intercostals, the rectus abdominis, transversus abdominis, and the internal and external obliques. The respiratory muscles are illustrated in Figure 2.1 and their corresponding levels of innervation from the spinal cord are shown in Table 2.1. The remainder of this section describes the mechanism by which the breathing muscles and the compliance of the lung affect ventilation. This information has been summarised from the respiratory physiology text book by West [150] and the exercise physiology text book by Katch et al. [79].

Quiet Breathing   Inhalation during quiet breathing is achieved by contraction of the diaphragm and the external intercostal muscles. The diaphragm is a dome shaped muscle which separates the thoracic and abdominal cavities and is inserted into the lower ribs. When the diaphragm contracts, its dome flattens out and displaces the abdominal contents downward, increasing the vertical dimension of the thorax. In addition, as the diaphragm moves downward, the abdominal

Figure 2.1 has been removed
due to copyright restrictions

Figure 2.1: The muscles of respiration [154]

Table 2.1: The muscles of respiration and their innervation

(a) The muscles of inspiration

Muscle	Innervation
Main	
Diaphragm	C3-C5
External intercostals	T1-T11
Accessory	
Scalene	C3-C8
Sternocleidomastoid	C2-C4

(b) The muscles of expiration

Muscle	Innervation
Rectus abdominis	T6 - T12
Transversus abdominis	T2 - L1
Internal and external obliques	T6-L1
Internal intercostals	T1-T11

contents act as a fulcrum. This allows the diaphragm to exert lateral appositional forces on the lower rib cage and increase the transverse diameter of the thorax.

The external intercostal muscles are situated between the ribs. When they contract the ribs are raised upward and forward, which increases the lateral and anterior-posterior diameters of the thorax. The volume increase of the thorax, resulting from contraction of the diaphragm and external intercostal muscles, creates a negative pressure gradient beween the atmosphere and the inside of the lungs, causing air to be inhaled. Exhalation during quiet breathing is a passive process. The lung and chest wall are elastic and upon relaxation of the inspiratory muscles they return to their natural equilibrium position. The reduction in dimensions of the thorax results in a positive pressure and air is expelled from the lungs.

Breathing During Exertion When the respiratory system is under stress, for example during exercise, ventilation has to increase to meet the additional metabolic demands of the body. To increase ventilation both the inspiratory and the expiratory muscles are used.

During exertion, a greater thoracic expansion compared with quiet breathing is observed. This is achieved both by additional activity in the diaphragm and intercostal muscles and by contraction of the inspiratory accessory muscles, which include the scalene and sternocleidomastoid muscles. These muscles are located in the neck and elevate the first two ribs and the sternum when they contract. Increased thoracic expansion causes an increased negative thoracic pressure and results in increased inhalation compared with quiet breathing.

As ventilation demands increase, passive exhalation switches to active exhalation. The main muscles of exhalation are the internal intercostal muscles and the abdominal wall muscles. When the internal intercostal muscles contract they work in the opposing direction to their external counterpart to reduce the anterior-posterior and lateral dimensions of the thorax. The abdominal wall consists of the rectus abdominis, transversus abdominis and the external and internal oblique muscles. When the abdominal muscles contract they push the diaphragm upward compressing the vertical dimension of the thorax. The action of the internal intercostal and abdominal wall muscles reduces the dimensions of the lung and chest wall past the end expiratory lung volume that is normal during quiet breathing. In turn, this causes a further increase in positive pressure and more air to be expelled from the lungs. The complement to this action is the passive recoil of the lungs and chest wall back to their equilibrium point which increases the air drawn into the lungs during the next inhalation.

Elasticity of the Lung and Chest Wall (Compliance)

The chest wall and the lung are both elastic and are divided by the intra-pleural space. At the end of exhalation during quiet breathing, the lung and the chest wall are in their natural equilibrium position. At this lung volume, known as Functional Residual Capacity (FRC), the intra-pleural pressure is negative. This resists the tendency of the lung to deflate and the tendency of the chest wall to spring out. As the lung inflates past FRC the intra-pleural pressure becomes more negative. As the lung volume deflates from FRC the intra-pleural pressure increases toward zero. The ratio between the change in unit volume of the lung for every change in unit pressure in the intra-pleural space is known as compliance. In the normal operating range of the lung, compliance is relatively high and the lung can be easily expanded or compressed by the respiratory muscles. However, at very high or very low lung volumes the compliance is reduced and it becomes much harder for the respiratory muscles to expand or compress the lungs. Compliance is an important aspect of ventilation because it determines how much work the breathing muscles need to do to expand or compress the lung. This information has been summarised from the text in the respiratory physiology text book by West [150] and the exercise physiology text book by Katch et al. [79].

2.1.3 Diffusion Across the Blood Gas Barrier

During inhalation, air is drawn in through the nose and mouth and initially flows through the conducting airways, which are made up of the trachea, the main bronchi and the terminal bronchioles. From the terminal bronchioles the air moves into the respiratory zone that consists of approximately 300 million small capillary wrapped air sacks, called alveoli.

In the alveoli, oxygen and carbon dioxide are transferred across the alveoli wall, or blood-gas barrier, by diffusion. In the blood that enters the capillary network around the alveoli, the partial pressure of oxygen is lower than that found in air and the partial pressure of carbon dioxide is higher than that found in air. These pressure gradients across the blood-gas barrier drive diffusion so that oxygen rich blood leaves the lungs and is carried to the rest of the body.

Alveolar Ventilation

Alveolar ventilation referes to the portion of air that is inhaled each breath which reaches the alveoli (i.e. the air in the respiratory zone). It is always less than the volume of air inhaled as diffusion does not occur in the anatomical dead

space, which includes the trachea, the main bronchi and the terminal bronchioles. During rapid and shallow breathing a greater proportion of the air that is inhaled is lost to the anatomical dead space compared with deep and slow breathing. Thus, deep and slow breathing represents a more efficient pattern of breathing.

Ventilation to Perfusion Ratio

The ventilation to perfusion ratio is the ratio of the volume of air to the volume of blood reaching the alveoli. Ideally, the amount of oxygen provided via ventilation to each alveoli would be enough to saturate the blood in the capillaries surrounding each alveoli. In reality alveoli can be either under-perfused, in which alveoli contain more oxygen than can be absorbed by the blood in the surrounding capillaries, or over-perfused, in which alveoli contain less oxygen than is required to saturate the blood in the surrounding capillaries. Under-perfused or over-perfused alveoli represent physiological dead spaces and represent a loss in breathing efficiency. This information in Section 2.1.3 has been summarised from the text in the respiratory physiology text book by West [150] and the exercise physiology text book by Katch et al. [79].

2.1.4 Non Respiratory Functions of the Lung

The lung is the organ which has the largest surface area in the body exposed to the external environment: consequently it is highly susceptible to damage by foreign material and infection. To compensate for this, the lung has both physical and immunological defense mechanisms.

A cough is an important physical defense mechanism which is used to clear foreign particles and mucus from the lungs after they have been transported to the trachea by mucociliary clearance. It is defined as a three phase motor action which begins with the patient making an inspiratory effort (inspiratory phase). This is followed by contraction of the expiratory muscles against a closed glottis allowing intrathoracic pressure to rise (compressive phase). In the final phase the glottis is opened causing a rapid expulsion of air from the lungs (expulsive phase) [114]. Without an effective cough, mucus becomes trapped in the lung and can lead to pneumonia, atelectasis and respiratory failure [106].

2.2 Respiratory Testing

To diagnose problems or to track changes over time, it is necessary to be able to quantify the different aspects of the respiratory system. Various tests have been developed to diagnose problems in, and track changes to, the respiratory system. The aspects measured include ventilation, diffusion, blood flow, ventilation-perfusion relationships, blood gases and pH, changes in the mechanics of breathing and the control of ventilation. An overview of these tests is given by West [150]. In this section a summary of both the lung volume measurements and the respiratory tests that are used in this thesis are given.

2.2.1 Lung Measurements

The volumes of the lung are shown in Figure 2.2. A description of the terms used in the figure follows:
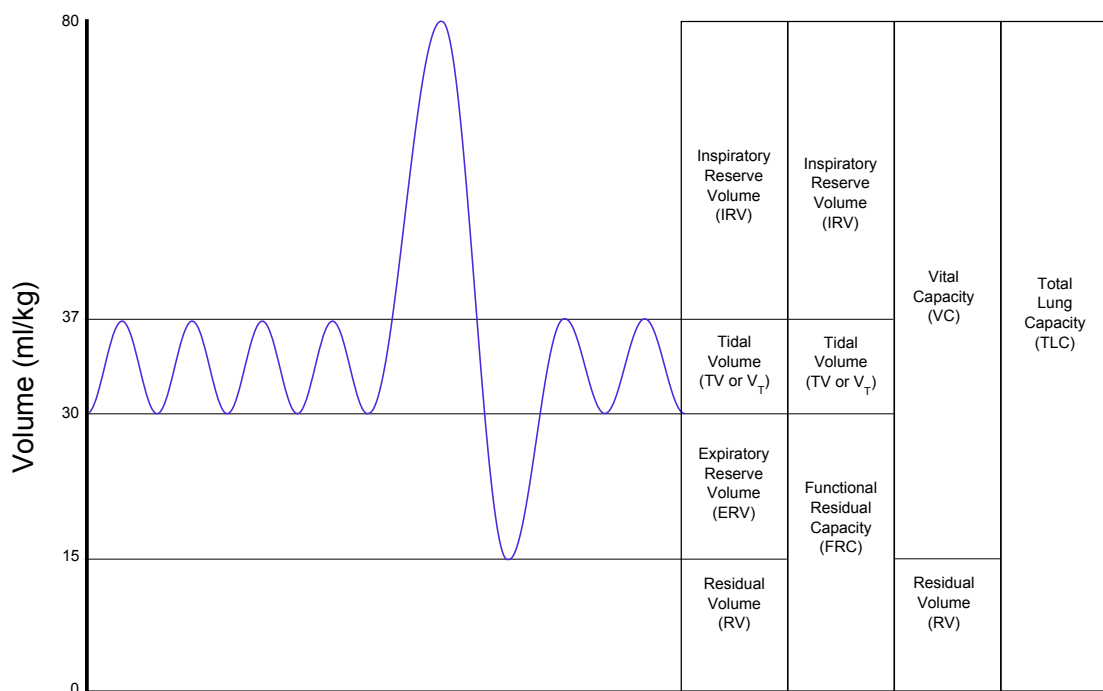
Figure 2.2: Standard lung volumes (adapted from wikipedia, http://en.wikipedia.org/wiki/File:Lungvolumes.svg)

Total lung capacity The maximum volume of air that can be contained within the lung.

Vital capacity The maximum volume of air that can be inhaled/exhaled following a maximum exhalation/inhalation.

Residual volume The volume of air that remains in the lung after maximum exhalation from TLC (TLC - vital capacity).

Tidal Volume (V_T) The volume of air inhaled or exhaled during normal quiet breathing.

Inspiratory Reserve Volume The extra volume of air that can be inspired at the end of quiet breathing inhalation.

Expiratory Reserve Volume The extra volume of air that can be expelled following quiet breathing exhalation.

Functional Residual Capacity (FRC) The total volume of air left in the lungs following quiet breathing exhalation (residual volume + expiratory reserve volume).

In addition to measuring lung volumes there are several other breathing parameters which are defined as follows:

Forced Vital Capacity (FVC) The maximum volume of air that can be exhaled when exhaling with maximum forced effort from a full inspiration.

Forced Exhaled Volume in One second (FEV_1) The volume of air exhaled in the first second of a forced expiration from a position of full inspiration.

Peak Expiratory Flow (PEF) The peak expiratory flow rate obtained during a forced exhalation from a position of full inspiration.

Cough Peak Flow (CPF) The peak expiratory flow rate obtained during a cough.

Maximum Expiratory Pressure (MEP) is the maximum expiratory pressure (commonly measured in centimeters of water (cmH_2O) that can be generated at the mouth and can be either measured from total lung capacity or FRC.

Breathing Rate (BR) The number of full breaths (inhalation and exhalation) taken every minute.

Minute Ventilation ($\dot{V}$) The total volume of air inhaled or exhaled every minute.

2.2.2 The Forced Vital Capacity Test

The FVC test is a simple and useful test of pulmonary function [112]. The main outcome measures from the test are FVC, FEV_1 and PEF which are described in Section 2.2.1.

To conduct the test the patient is asked to inhale to total lung capacity before exhaling as quickly and completely as possible. This is repeated, up to eight times, until three acceptable manoeuvres have been collected. Acceptable repeatability is achieved when the difference between the largest and the next largest FVC is less than or equal to 0.15 L, and the difference between the largest and next largest FEV_1 is less than or equal to 0.15 L. The best outcome measures from the three acceptable manoeuvres are taken as the overall test result. The test is usually conducted using a hand-held spirometer according to the guidelines published by the American Thoracic Society (ATS) and European Respiratory Society (ERS) [112], which were written to ensure reliability in the general population. The work carried out by Kelley et al. [80] found that the FVC test guidelines could be used reliably in SCI, although it should be noted that his investigation only included patients who were at least one year post injury.

Despite the findings of Kelley et al. [80] several studies which measure respiratory function in tetraplegia using the FVC test have used the best result from three attempts rather than following the ATS/ERS guidelines [27, 70, 159].

When the FVC test is applied to SCI patients the outcome measures are commonly expressed as a percentage of the predicted values for a healthy subject calculated by reference equations based on age, sex, height and race [69]. Accordingly it can used both as a diagnostic tool to measure the effect of disease on pulmonary function and as a monitoring tool to assess therapeutic intervention [112].

2.2.3 The Maximum Expiratory Pressure Test

MEP is a straightforward and convenient index of respiratory muscle strength. The guidelines set out by the ATS/ERS [53] specify that it should be measured at the mouth using a pressure transducer but they allow for significant differences in methodology, which makes the comparison of studies difficult.

The two major differences are:

1. Whether a flanged or tube type mouthpiece is used. MEP is greatest when measured using a flanged mouthpiece (the recommended mouthpiece) as it ensures a lower leak, particularly for subjects with severe respiratory

weakness [53].

2. Whether the test is conducted from total lung capacity or from FRC. MEP is greater when measured from total lung capacity, the method used in the majority of studies [66, 113, 145].

2.2.4 Assessment of Cough

The effectiveness of a cough is most commonly assessed using CPF [9]. A CPF of 160 L/min (2.7 L/s) is regarded as the minimum required to clear secretions effectively and it has been shown that patients with a CPF of at least 270 L/min (4.5 L/s) are significantly less likely to develop pneumonia [146]. CPF is highly dependent on the pressure that is generated during the glottal closure phase of the cough [41]. MEP is therefore also useful in assessing cough efficacy. In addition, some cough studies also report gastric pressure and oesophageal pressure as outcome measures [24, 87, 104].

There is considerable variation in the methodology that has been used across cough studies. Important variables in the measurement of cough include inhalation volume, subject position and the measurement protocol.

Cough inhalation volume has been the most inconsistent factor between studies. Studies have chosen to measure either the maximum cough effort without controlling for inhalation volume [57], or the maximum effort from total lung capacity [24], or to measure cough from FRC [92]. Inhalation volume of a cough is an important variable since the recoil force of the lung increases with increasing lung volume. This is illustrated by Di Marco et al. who showed that airway pressure generated using SCS was smaller at FRC compared with total lung capacity [41].

The majority of studies have measured cough while the patient is sitting (for example, Gollee et al. [57] and Butler et al. [24]), however, there have been investigations in which the patient was supine (for example, Jaeger et al. [75]). This variable is important because lung mechanics are substantially different between the supine and sitting position (see Section 2.3.4).

The measurement protocol for cough has included either taking the best of three attempts (for example, Butler et al. [24]) or taking the mean of several attempts (for example, Gollee et al. [58] and Jaeger et al. [75]). There are advantages and disadvantages to each approach. It is theoretically not possible to overestimate a measure of maximum capacity but taking the mean over several attempts reduces the possibility of measurement errors, which are unavoidable in

a practical setting.

2.2.5 Quiet Breathing Measurement

The outcome measures that are commonly used to characterise quiet breathing are V_T, BR and $\dot{V}$. Less commonly, breathing gases, such as End Tidal Carbon Dioxide (ET_{CO_2}), have also been measured. There is no standard protocol for the assessment of quiet breathing. Previous studies have typically compared short periods (for example 30s [134]) of unassisted and AFES-assisted breathing.

End-Tidal Carbon Dioxide Measurement

ET_{CO_2} is a surrogate measure of the partial pressure of carbon dioxide in the alveoli and in the arteries and can be used to determine alveolar ventilation [110]. The partial pressure of carbon dioxide in the arteries is inversely proportional to the alveolar ventilation. For example, if the partial pressure of carbon dioxide in the arteries doubles then the alveolar ventilation is halved, all other factors being equal [150]. The other factors which influence the partial pressure of carbon dioxide in the arteries include metabolic rate, cardiac output and body temperature.

2.3 The Respiratory System in Tetraplegia

The respiratory system is severely compromised in patients with tetraplegia as a result of breathing muscle paralysis (Section 2.3.1), muscle atrophy (Section 2.3.2), and changes in the mechanical properties of the lung (Section 2.3.3). The extent to which these changes affect the function of the respiratory system can clearly be observed in spirometry measurements (Section 2.3.4), assessment of cough (Section 2.3.5) and assessment of quiet breathing (Section 2.3.6).

2.3.1 Breathing Muscle Paralysis

Most tetraplegic patients will suffer from paralysis of their breathing muscles [154]. The extent of the paralysis will depend on the neurological level and completeness of the SCI. The completeness of an injury is commonly assessed using the ASIA Impairment Scale (AIS), which is explained in Table 2.2 below. The neurological level of SCI is defined as the most posterior segment of the spinal cord in which normal motor and sensory function on both sides of the body remain [103].

In all patients with a motor complete tetraplegic injury, the intercostal muscles (innervated from T1-T11) and the abdominal wall muscles (innervated from T6-L1) will be paralysed. As the level of tetraplegic SCI moves further up the cervical region of the spinal cord, the latissimus dorsi (innervated from C6-C8), pectoralis major (innervated between C5-C7), scalene (innervated from C3-C8) and sternocleidomastoid (innervated from between C2-C4) may also become paralysed. At injuries above C5, diaphragm function will be affected. In motor complete tetraplegia above C3, the diaphragm will be completely paralysed and the patient will be unable to breathe without mechanical ventilation.

Table 2.2: Grades of the AIS

Grade	Description
A	Motor complete. No Sensory or motor function is preserved in the sacral segments S4-S5. (This includes anal sensation).
B	Motor complete. Sensory but no motor function is preserved below the neurological level and includes the sacral segments (this includes contraction of the external anal sphincter).
C	Motor incomplete. Motor function is preserved below the neurological level, and more than half of the key muscles below the neurological level do not have full range of motion against gravity.
D	Motor incomplete. Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have full range of motion against gravity.
E	Normal. Sensory and motor function is normal.

2.3.2 Muscle Atrophy in Spinal Cord Injury

Respiration in tetraplegia is also affected by muscle atrophy [72], which is a major secondary complication following a SCI [63, 118]. The primary consequences of muscle atrophy in SCI are a change in the composition and a reduction in the cross sectional area of a patient's muscle [26, 51, 63, 118].

The change in muscle composition following a SCI is observed as a change in the relative constituents of the different types of muscle fibres that make up skeletal muscle [26, 118, 142]. There are three muscle fibre types: Type 1, Type 2A and Type 2X [118, 123].

- Type 1 fibres rely predominately on oxidative metabolism; they contract slowly and are resistant to fatigue.

- Type 2A fibres rely on a mix of oxidative and anaerobic metabolism; they are fast-contracting and fatigue resistant.
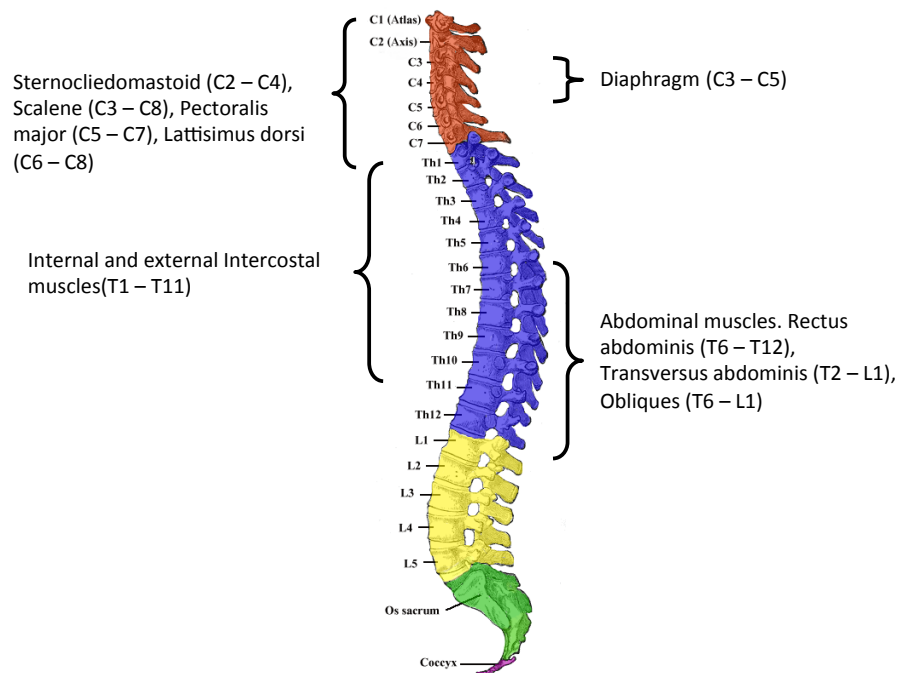
Figure 2.3: The innervation of the respiratory muscles. (Accessed 2nd June 2014 from Wikimedia Commons http://commons.wikimedia.org/wiki/File:Gray_111_-_Vertebral_column-coloured.png)

- Type 2X fibres rely predominately on anaerobic metabolism; they are fast-contracting and susceptible to fatigue.

The range in muscle fibre types allows a variety of tasks to be completed efficiently. Slow contracting muscles fibres are recruited mainly for tasks that have to be sustained over a long period but which do not require a large force or speed of contraction, e.g. maintaing posture. Fast contracting fibres are recruited for tasks which require rapid forceful contractions that are not sustained e.g. jumping [123].

Following a SCI, there is a shift in the relative constituents of the muscle fibres, which results in a higher relative proportion of Type 2A muscle fibres than other muscle fibre types [118]. The mechanism by which this occurs is not clear. Some studies have found that the number of Type 1 and Type 2X fibres decrease. Other studies have only found a reduction in the number of Type 2X fibres without a corresponding change in the number of Type 1 fibres [26].

The magnitude of the reduction in muscle cross sectional area following a SCI is known to vary depending on the muscle and the level of injury [118]. To date studies investigating the effects of disuse atrophy have concentrated on the muscles of the leg [26, 64] or arm [142]. However, Estenne et al., demonstrated a 34% reduction in the thickness of the abdominal-wall muscles in patients with

tetraplegia [51]. Furthermore, Kowalski et al. showed a reduction in the cross sectional area and a shift in the fibre type composition of the internal and external oblique, internal intercostal and transversus abdominis muscles in spinalised cats [82].

The major clinical implication of muscle atrophy and muscle fibre type conversion is a reduction in fatigue resistance of the muscle. This can affect a patient's ability to complete activities of daily living, inhibit the effectiveness of rehabilitation programs and decrease overall quality of life [118].

2.3.3 Compliance and the Work of Breathing

A tetraplegic patient's ability to ventilate the lung is severely compromised by changes in lung-chest wall compliance and by changes in the mechanics of breathing.

In the two weeks following tetraplegic SCI, an inward movement of the chest, which is paradoxical to the outward distension of the abdomen, can be observed during inhalation. The collapse of the chest results from intercostal muscle paralysis and reduces the effectiveness of the diaphragm in expanding the thorax and inhaling air into the lungs [12]. Paradoxical chest movement becomes less common within two weeks to one month after SCI [126] as a result of:

- increased strength of the accessory muscles (scalene and sternocliedomastoid) which are recruited to support the upper chest wall during inhalation [54].

- A reduction in overall compliance of the respiratory system [48, 54]. The reduction in overall compliance resists the tendency for the chest wall to collapse during diaphragm excursion [35]. The reduction may be caused changes in the surfactant in the lung, a stiffening of the rib cage, ankylosis of the rib cage joints [48, 54, 126], and spasticity of the intercostal muscles [54, 126].

Although there is a reduction in chest wall compliance as the injury progresses, the thoracic-abdominal wall compliance is elevated by 170% in tetraplegic patients compared with healthy individuals [48]. As a result, the biggest contribution to tidal volume in tetraplegia is from volume changes in the abdominal compartment [48]. The increased abdominal compliance reduces the fulcrum effect of the diaphragm contracting against the abdominal contents and thus limits the diaphragms ability expand the lower rib cage. [48, 154]

The effect of the reduction in chest-wall compliance and increase in thoracic-abdominal wall compliance for a patient with tetraplegia is an increased work of breathing that increases the load placed on the respiratory muscles compared with healthy subjects [127].

2.3.4   Measured Changes in Spirometry

The effect of tetraplegia on ventilation can be clearly observed in measurements of FVC, FEV_1, PEF, MEP and maximum inspiratory pressure, which are reduced considerably compared with a healthy population (see Table 2.3 for example values) [66, 76, 86, 94, 102, 113, 115, 136, 138, 145, 148]. These measures are most affected in patients with the highest levels of SCI who suffer from the greatest degree of paralysis [94, 102, 148].

Table 2.3: Pulmonary function measures in patients with tetraplegia. FVC, FEV_1, and PEF were taken from the study by Cheng et al. [27]. MEP and maximum inspiratory pressure were taken from the study by Mateus et al. [102]. %pred.: percentage of the predicted value for a healthy subject (see Section 2.2.2); MIP: maximum expiratory pressure

Measure	Absolute value	%pred.	Reference
FVC	1.79 L	39.2	Cheng et al. [27]
FEV_1	1.74 L	48.9	Cheng et al. [27]
PEF	2.91 L/s	36.3	Cheng et al. [27]
MIP	45.36 cmH_2O	57.6	Mateus et al. [102]
MEP	69.04 cmH_2O	24	Mateus et al. [102]

Pulmonary function measurements are at their lowest during the three weeks immediately following an injury. Thereafter they can increase considerably within the first year of injury [86, 115], possibly as a result of the increased chest wall compliance (see Section 2.3.3) [86, 115] and increased levels of physical activity [115]. After the first year of injury there is a decline in pulmonary function measurement which is related to time post injury, age and continued smoking [76, 94, 138] but unrelated to the level and severity of injury [138].

Effect of Posture

In an able-bodied individual, vital capacity usually decreases slightly when moving from a seated to a supine posture. However, in tetraplegia, vital capacity is greatest in the supine position and decreases as a patient's upper body becomes more upright [10, 49].

2.3.5   Effect of Tetraplegia on Cough

Tetraplegia affects both the compressive and the expulsive phases of the cough. During the compressive phase, both the paralysis of the main expiratory muscles (the abdominal and internal intercostal muscles) and the reduced vital capacity in tetraplegic patients which restricts the lung recoil force, limit the intra-thoracic pressure generated [117]. In turn the reduced intra-thoracic pressure limits the CPF that is generated during the expulsive phase of the cough.

Conventional thinking assumes that the passive recoil of the lung is the only mechanism by which tetraplegic patients generate intra-thoracic pressure during a cough. However, it has been shown that patients can contract the latissimus dorsi and clavicular portion of the pectoralis major muscles to achieve active expiration [50, 52, 144].

The generation of CPF in tetraplegia is significantly related to the neurological level of SCI [148]. It has been reported to be between 1.86 L/s to 4.73 L/s (see Table 2.4 on page 42) which is less than half the 8.7 L/s reported in healthy subjects [125].

2.3.6   Effect of Tetraplegia on Quiet Breathing

In tetraplegic patients who are still able to breathe spontaneously, V_T during resting breathing has been shown to be significantly lower than in the able-bodied population [18]. In some patients the reduced V_T is compensated by an increase in BR resulting in a $\dot{V}$ that is similar to the able-bodied population. In other patients, however, BR is similar or reduced, and thus $\dot{V}$ is reduced, compared with the able-bodied population [18]. Maximum voluntary ventilation is also considerably lower in patients with tetraplegia (78 L/min [109]) compared with able bodied controls (140-160 L/min [79]).

2.4   Functional Electrical Stimulation

FES is a technique that can be employed to elicit a non-voluntary contraction of skeletal muscles. For many years it has been used on patients with SCI in a wide range of applications including arm cranking exercise for tetraplegic patients [33] and paraplegic cycling for paraplegic patients [14]. This thesis focuses on the use of AFES as a method of enhancing respiratory function in patients with tetraplegia. This section gives an overview of the important general aspects of FES, while Section 2.5 discusses the specific aspects of AFES.

2.4.1 Stimulation Parameters

The strength of the muscle contraction generated using FES is governed by three main stimulation parameters: stimulation current, stimulation frequency and stimulation pulse-width (illustrated in Figure 2.4) [15]. Previous research has shown that progressive increases in either the stimulation current or pulse-width increases the number of motor fibres recruited in the arm or leg muscle groups. Progressive increases in stimulation frequency increase the torque produced per active fibre [130].

$$Frequency = \frac{1}{pulse\ period}$$
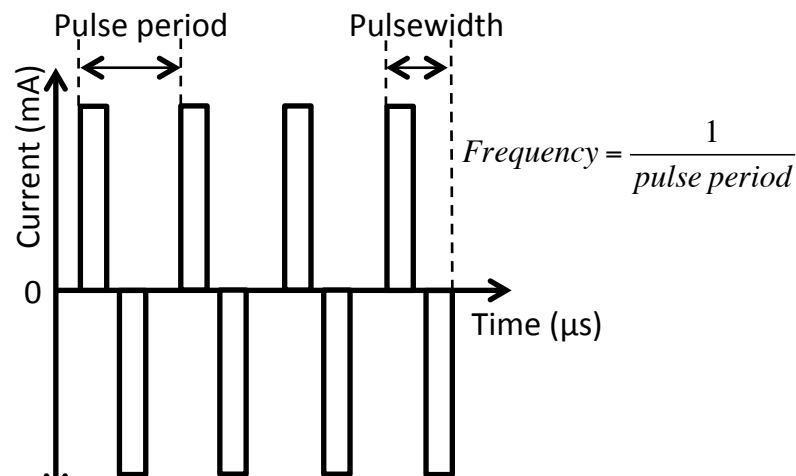
Figure 2.4: Stimulation waveform parameters

In the majority of FES stimulators that are currently available, the stimulation pulses within a stimulation train are delivered at a constant frequency. This is known as Constant Frequency Train (CFT) stimulation and is illustrated in Figure 2.4. Catchlike Inducing Frequency Trains (CITs) are another type of stimulation train that is being researched. They include an initial two pulse burst (called a doublet) that are delivered at a higher frequency than the remainder of the pulses in the train (Figure 2.5). It has been shown that CITs can increase the force production of electrically stimulated muscle compared with CFTs [16].

There is a paucity of research that has investigated the effect of modulating the stimulation parameters on abdominal muscle contraction. However, two studies have demonstrated that a positive linear relationship exists between stimulation current and twitch gastric pressure [24, 88]. Since gastric pressure is directly related to the strength of abdominal muscle contraction, this suggests that the strength of abdominal muscle contraction is also related to the stimulation current.
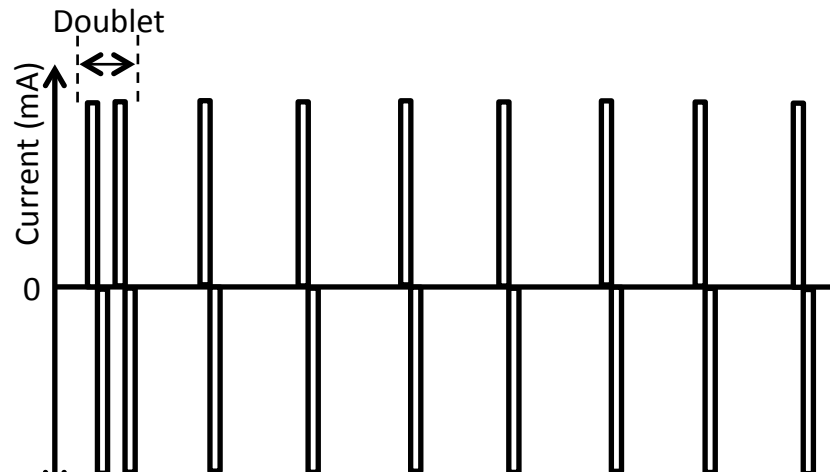
Figure 2.5: Catchlike inducing stimulation train

2.4.2 Muscle Recruitment During Functional Electrical Stimulation

Type 1 fibres contract mainly using aerobic metabolism, Type 2x fibres contract mainly using anaerobic metabolism and Type 2A contract using both aerobic and anaerobic metabolisms. Anaerobic metabolism relies on fast glycolysis, which allows the muscle to contract quickly but is less metabolically efficient than aerobic metabolism. As a result Type 2X muscle fibres fatigue quicker than Type 1 muscle fibre types [79]. During a normal physiological contraction controlled by the central nervous system, muscle fibres are activated according to the Henneman size principle [15, 123]. This principle states that Type 1 fibres are recruited during slow moving tasks that require a small amount of force. As the speed and force required for a task increases, additional fibre recruitment includes Type 2A fibres and subsequently Type 2X fibres. The size principle ensures that a muscle contraction uses a little anaerobic metabolism as possible to achieve a given task (i.e. it is metabolically optimal) [15, 123, 130].

There are two major differences in the muscle fibre recruitment pattern when a contraction is elicited using transcutaneous FES.

1. When using transcutaneous FES only those muscle fibres located within the electrical field produced by the stimulation are activated [15]. Consequently, for a given stimulation intensity the same group of muscle fibres is activated repeatedly, i.e. the recruitment is spatially fixed. By contrast, physiologically normal contractions recruit a range of fibres that are innervated by motor nerves that are not necessarily proximal to the surface of the skin. In addition consecutive contractions of the same overall output

may be realised by different muscle fibres i.e. recruitment is not spatially fixed.

2. When using FES, within the group of muscle fibres reached by the stimulation field, activation is not specific and the activation of the different fibre types is random [15]. This is intrinsically different from the recruitment order of muscle fibres specified by the Henneman size principle and is not metabolically optimal.

Both of these differences result in a higher rate of fatigue during an FES evoked contraction compared with a physiologically normal contraction.

2.4.3 Muscle Fatigue

Muscle fatigue is a major limitation when using FES in SCI. It is partially a result of the muscle fibre recruitment pattern, described above, and partially caused by the disuse atrophy of the muscles [15, 118].

It is possible to defer the onset of fatigue by increasing the stimulation intensity (either via current or pulse-width) or by increasing stimulation frequency [29, 67]. While increasing stimulation intensity increases the number of motor fibres recruited (by increasing the penetration of the stimulation field), it also continues to recruit the fibres close the stimulation site. Increasing the stimulation frequency increases the force output of the activated fibres. Both strategies do not allow motor fibres to recover and complete fatigue of the muscle is inevitable.

Kandare et al. [78] have been the only authors to have studied this aspect when using AFES. In a single patient, they found an approximately linear negative relationship between tidal volume and cumulative number of AFES-assisted breaths.

2.4.4 Autonomic Dysreflexia

A potentially serious side effect of FES is autonomic dysreflexia. Autonomic dysreflexia is a result of disruption to the autonomic nervous system whose symptoms include anxiety, sweating and headache. In extreme cases autonomic dysreflexia can be fatal. Autonomic dysreflexia only occurs in patients with an injury above the T6 level of the spinal cord. It is triggered when nociceptive stimulus below the level of SCI, causes a reflex induced sympathetic discharge. This discharge causes vasoconstriction which in turn leads to hypertension. The physiologically

normal response to hypertension is to stimulate baroreceptors to induce a compensatory response that includes bradycardia and vasodilation. However since the fibres that stimulate vasodilation are unable to cross the site of SCI, hypertension below the level of injury persists until the nociceptive stimulus ceases [7, 83].

Autonomic dysreflexia is normally caused by irritation of the gastrointestinal tract and bladder. However, since transcutaneous FES results in stimulation of the sensory nerves, in addition to the motor nerves, it can also trigger autonomic dysreflexia [7].

2.5 Abdominal Functional Electrical Stimulation Technology

There have been several different approaches to the implementation of AFES to improve respiratory function in tetraplegia. In this section the two basic AFES paradigms are introduced and the technological approaches described.

2.5.1 Abdominal Functional Electrical Stimulation Paradigms

The application of AFES to improve respiratory function can be divided into two basic paradigms: neuro-prosthesis applications and neuromuscular retraining [5]. When using AFES as a respiratory neuro-prosthesis, a patient's unassisted respiratory function is temporarily improved while their abdominal muscles are being stimulated [58]. In contrast, neuromuscular training refers to an intervention, made up of regular sessions of AFES applied over a period of several weeks, with the goal of improving a patient's unassisted respiratory function [27].

The majority of AFES research has been focussed on using AFES as a respiratory neuro-prosthesis (Section 2.7). Under this paradigm, previous authors have been focussed on a common aim: developing an assistive device that can be used in tetraplegia to reduce respiratory complications. The first step in achieving this goal is to determine the acute effect of AFES on key ventilatory parameters. This step has been well researched and it is known that AFES can be used to enhance: FVC, FEV_1, PEF, and MEP (see Section 2.7.1); CPF (see Section 2.7.2); and V_T (see Section 2.7.3). The next logical step is to investigate the effects of chronic use of AFES as a neuro-prosthesis. In other words, what impact does using AFES over a period of time (e.g. three to four weeks) have on AFES-assisted breathing parameters? Since SCI is associated with muscle disuse atrophy and muscle fibre remodeling, chronic use of AFES may result in muscle adaptions that improve

(or reduce) the acute benefits of AFES. As will become evident in Section 2.7.1 to Section 2.7.3 there is a paucity of research on this topic.

There is limited evidence emerging that AFES neuromuscular training improves unassisted respiratory function in tetraplegia (see Section 2.8). An advantage of this paradigm is that after the training programme, the patient benefits from improved respiratory function without having to use an external aid. However, an important consideration and potential limitation of this paradigm is its ability to be implemented within a normal pulmonary rehabilitation programme.

2.5.2 Technological Implementation of Abdominal Functional Electrical Stimulation

The fundamental components of an AFES system include:

- a sensor to measure a patients breathing pattern

- a controller that triggers stimulation in synchrony with a patients volitional exhalation

- a stimulator that generates the desired stimulation waveform output

- stimulation electrodes that deliver stimulation to the abdominal wall muscles

These fundamental components are illustrated in the system schematic shown in Figure 2.6.

The implementation of AFES has varied across different research studies, ranging from the most basic approach, where an operator visually monitors a patients breathing activity and manually activates stimulation (for example, the work by Butler et al. [24]), to more elaborate approaches, in which a patient's respiratory activity is measured by a sensor and stimulation is automatically applied to the abdominal muscles using a computer as the controller (for example, the work by Gollee et al. [57]).

2.5.3 Stimulation Electrodes

While the majority of research studies have used two stimulation channels with electrodes placed over the rectus abdominis muscle group [75,87,133,140], Gollee et al. [57,58] used four channels with electrodes placed over the rectus abdominis and external oblique muscles, and Butler et al. [24] used two channels with
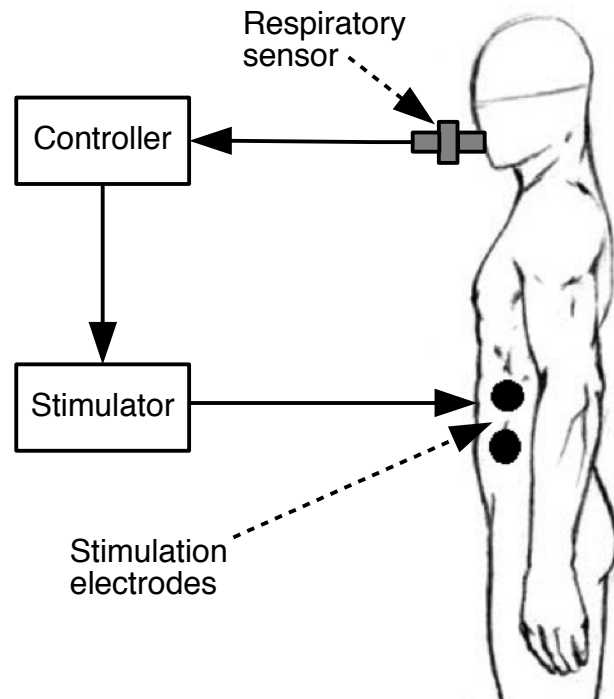
Figure 2.6: A schematic of the fundamental components of an AFES system

electrodes placed posterolaterally. Figure 2.1 on page 13 illustrates the breathing muscles and Figure 2.7 illustrates the different electrode positions.

(a) Rectus abdominis (shown as grey) and external oblique (shown as black) electrode placement

(b)   Postereolateral   electrode position
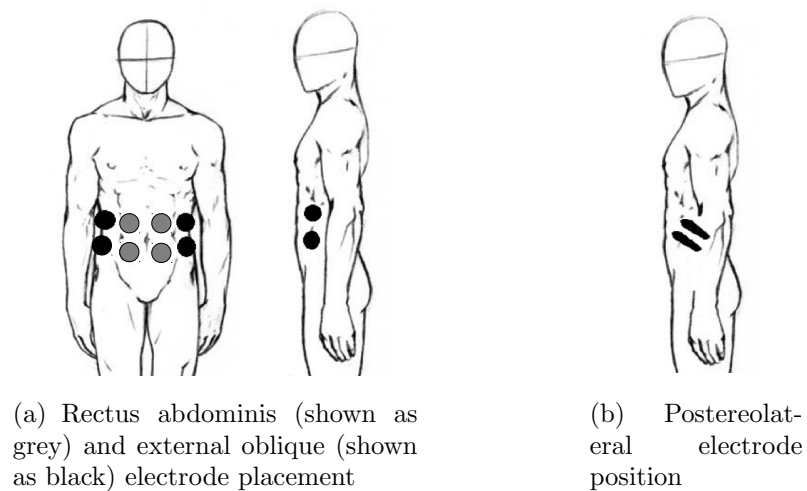
Figure 2.7: Position of the stimulation electrode electrodes used in previous research studies.

There is debate as to which electrode position is optimal for AFES. The study by Kandare et al. was the first to investigate the effect of the number of electrodes and the electrode position [78]. This study, which included a single

tetraplegic patient, found that the combined stimulation of the rectus abdominis and the external oblique muscles was more effective than stimulation of either of the muscle groups individually.

The optimal electrode position for AFES has been further researched in groups of healthy subjects. Lim et al. [88] measured twitch gastric pressures while stimulating the abdominal muscles using two channels. They found that electrodes placed posterolaterally evoked greater pressures than electrodes placed over the rectus abdominis for a given stimulation intensity. Subsequent work by Gollee and Henderson [56] measured change in abdominal circumference with stimulating electrodes placed either over the rectus abdominis, or external oblique muscles, or posterolaterally, or in combinations of the above. They found that electrodes placed either over the external oblique muscles or posterolaterally resulted in the strongest response. They also found that the optimum configuration varied between subjects.

The results from the studies cited above are difficult to compare directly as there are significant methodological differences between them. For example, Lim et al [88] assessed the positions using gastric pressure whereas Gollee and Henderson [56] measured abdominal movement. Further work is required to determine which is the most effective electrode position overall. It is likely that the optimal electrode position will vary between patients and that an optimum position will have to be established for each individual.

2.5.4 Control Strategies

The majority of studies that have investigated the clinical effects of AFES have used commercially available stimulation systems which allow the user to control the timing of stimulation with a pushbutton. In these studies, stimulation has been controlled either by the researcher (for example the work by Langbein et al. [85]) or by the patient (for example the work by Butler et al. [24]). The effectiveness of AFES to improve unassisted respiratory function has been shown to be independent of the manual operator [24].

There are a limited number of studies which have developed and used automatic approaches to the control of AFES [57, 61, 78, 132, 133].

Sorli et al. [132] were the first to report a system that applied AFES automatically in synchrony with a patient's volitional exhalation. In this system, air flow rate was measured at the mouth using a pneumotachograph. A microcontroller monitored the flow rate and generated a one second stimulation trigger when the flow rate reached 15% of a pre-calibrated maximum. A similar system was used

by Kandare et al. [78] when they investigated the effects of AFES on breathing volumes in tetraplegic patients with diaphragm paralysis.

The two systems described by Sorli et al. [132] and Kandare et al. [78] were successful in augmenting unassisted V_T in patients but were not suitable for assisting cough. Spivak et al. [133] used the finding that tetraplegic patients can contract the clavicular portion of the pectoralis major during coughing [50, 52, 144], to design an automatic AFES system to assist coughing. That system triggered stimulation according to the activity of the pectoralis major muscle, measured using electromyography.

A major limitation of these automatic AFES systems is that they can be used to assist only one type of breathing activity. Gollee et al. developed a system which could be used to assist both quiet breathing and coughing [57]. In addition this system could aimed prevent unwanted stimulation by automatically muting stimulation during speech. The system classified quiet breathing successfully but was less successful in differentiating between deep breathing and an attempt to cough.

A subsequent control system developed by Gollee et al. used a steady state visual evoked potential brain computer interface [61]. Brian computer interface technology allows for a novel, non-neuromuscular pathway for communication and control [155]. A steady state visual evoked potential type brain computer interface can infer a user's intent by detecting their visual attention to one of a panel of rapidly oscillating light sources [4]. The AFES brain computer interface system developed by Gollee et al. allowed accurate switching between different stimulation modes (quiet breathing, cough or mute). In addition, this was the first AFES system which allowed the user to increase the stimulation intensity to account for abdominal muscle fatigue. While brain computer interface systems are rapidly progressing they currently remain confined to the research domain. This approach is, therefore, unlikely to become a practical option in the near future.

2.5.5 Respiratory Sensors

An integral component of the systems described above is the measurement of respiratory activity. In previous studies both the sensor used and the type of signal measured have had practical drawbacks. A measurement of air flow rate at the patient's mouth provides an accurate measure of a patient's respiratory activity. Its application is limited as it requires a patient to wear a sensor over

the mouth which restricts the ability to eat or speak. electromyography measurement of the pectoralis major only provides a useful signal for triggering cough as these muscles are not active during quiet breathing. To address these drawbacks, several researchers have evaluated alternative respiratory sensors for the purpose of triggering AFES [55, 60].

Gollee and Chen [55] used an inertial measurement unit attached to a belt around the abdomen. The results of this study showed that the inertial measurement unit output was able to distinguish between quiet breathing and a cough. However, an inertial measurement unit would also be sensitive to other movements in addition to those produced by breathing.

Gollee and Mann [60] used piezoelectric effort belts worn around the chest and the abdomen to measure breathing. This study showed qualitatively that the combined signal from the abdominal and chest belts closely followed the air flow rate measured by a spirometer. However, no quantitative analysis was performed and the data was collected only from healthy subjects.

Inertial measurement units and piezoelectric belts have been the only non-invasive respiratory sensors that have been investigated in the context of AFES. There are several other non-invasive respiratory sensors that could also be used to trigger AFES including respiratory inductive plethysmographs [31], fibre optic plethysmographs [8, 34], and nasal thermocouples [99].

2.5.6 Methods of Evaluation

In previous studies, the performance of a complete AFES system has either not been reported [132], or been reported only qualitatively [57, 133]. Respiratory sensors, which are possible alternatives to a spirometer, have been evaluated either qualitatively [60], or quantified by comparing the signal peaks during inhalation and exhalation for different breathing modes (eg. coughing and quiet breathing) [55]. There have been no previous studies which have evaluated the phase delay of AFES systems or alternative respiratory sensors.

In the authors opinion there are three key metrics that should be used to quantify the performance of an automatic AFES system: sensitivity, error rate, and phase delay. Sensitivity and error rate describe the accuracy of a system to apply stimulation for a given breathing pattern. For example, quiet breathing sensitivity is the ratio of the number of correctly stimulated breaths over the total number of breaths performed by a subject. Quiet breathing error rate is the ratio of the number of falsely stimulated breaths over the total number of breaths performed by a subject. Phase delay is the delay between the desired

start of stimulation and the actual start of stimulation. For example, during quiet breathing the phase delay is the temporal difference between the start of exhalation and the start of stimulation.

2.5.7 Discussion

Section 2.5.4 presented several different approaches to the control of AFES. Of these approaches, the author believes that applying stimulation automatically during cough and quiet breathing while muting stimulation during speaking [57] is the most practical solution when considering the use of AFES as a respiratory neuro-prosthesis. Currently one of the biggest drawbacks is its reliance on the measurement of air flow rate using a spirometer. In Section 2.5.5, non-invasive, alternative sensors to a spirometer were presented. Based on the current literature, piezo-electric belts worn around the abdomen and chest appear to be the best replacement for the spirometer. However, there are several other non-invasive sensors currently used in other fields that have not been investigated in the context of AFES and previous research has not properly quantified and compared the performance of the alternative sensors investigated with the spirometer. Quantification of the phase delay between an alternative sensor and the spirometer is particularly important for AFES-assisted cough as CPF is generated at the beginning of exhalation.

Previous research has focused on the technological challenges of using AFES as a respiratory neuro-prosthesis where the ability to distinguish between quiet breathing, speech and coughing is key. On the other hand, if AFES is used as a rehabilitation device as outlined in Section 2.5, the main functional requirement is the ability to apply stimulation in synchrony with the patient's volitional breathing. Coughing or other breathing patterns could be controlled using a simple on-off switch. These requirements could be met by using the approach outlined by Sorli et al. in Section 2.5.4 combined with one of the non-invasive sensors described in Section 2.5.5.

2.6 Alternatives to Abdominal Functional Electrical Stimulation

There are several other forms of neuro-prosthesis which have been used or could be used to improve respiratory function in tetraplegia. These include percutaneous FES, implanted FES, SCS and FMS. All of these techniques initiate an action

potential which propagates down the motor nerve to the neuromuscular junction. However, the means by which the action potential is generated differs between the approaches and each technology has advantages and disadvantages associated with its implementation.

2.6.1 Percutaneous Functional Electrical Stimulation

Percutaneous electrodes are minimally invasive needle electrodes which penetrate the skin and can be used to stimulate motor nerves directly [130]. Stimulation is more specific than transcutaneous FES and does not result in stimulation of the sensory nerves. Furthermore, since the electrodes can be used to stimulate specific motor nerves, it is possible to achieve finer control of the stimulated muscle. The limitations of the technology include electrodes breaking and infections occurring at the electrode skin junction. As a result, percutaneous FES systems are used mainly in research before a fully implanted system is considered [130]. As far as the author is aware, there have been no previous studies that have used percutaneous FES as a means to improve respiratory function in tetraplegia.

2.6.2 Implanted Functional Electrical Stimulation

Implanted systems are suitable only in applications where long-term use is envisaged [130]. The implanted components of these systems include electrodes, leads and a stimulator unit. The stimulator is charged and controlled by an external unit through a radio-frequency telemetry link. The electrodes can be placed either on to the muscle (epimysial electrodes) or on to the nerve supplying the muscle (cuff electrodes) [130]. Implanted phrenic nerve stimulators are a widely used alternative to chronic MV in tetraplegic patients who have diaphragm paralysis [71].

2.6.3 Spinal Cord Stimulation

SCS is another type of implanted electrical stimulation [39–41]. The electrodes for SCS are placed in the epidural space and stimulate the spinal cord ventral roots. As with percutaneous electrodes, the advantage of implanted systems over transcutaneous stimulation is improved stimulation specificity. Problems associated with implanted systems relate to biocompatibility of the implanted materials, electrode displacement, and electrode lead breakage. Currently SCS is being investigated by DiMarco et al. [39–41] as a means of improving cough in tetraplegic patients.

2.6.4 Functional Magnetic Stimulation

FMS uses the principles of magnetic induction to generate an electrical current in nerve fibres. The equipment consists of a magnetic stimulator connected to a coil. The coil is generally placed over the spinal cord at the level which corresponds with the muscles that are to be stimulated. The advantages of FMS are that it is easy to apply (since the coil can be placed over clothes), it is painless, and, compared to transcutaneous FES, a more complete activation of the muscle can be achieved. The limitation of FMS is that the equipment is bulky and relies on mains supply voltages [38]. There have been several studies that have investigated the use of FMS to improve respiratory function in tetraplegia (see Section 2.7 and Section 2.8).

2.6.5 Neuro-Prosthesis Comparison

Implanted FES, FMS and SCS are most effective at activating a muscle completely but have practical limitations. Presently, the need for a mains power source and bulky equipment mean that FMS is unlikely to be suitable for a practical neuro-prosthesis. Due to the inherent safety concerns of implanted systems, it is likely that implanted FES and SCS will be considered only for patients with the most severe problems. Transcutaneous FES, too, has practical limitations but the simplicity of the equipment and ease of application have led to its widespread use in research and commercial settings.

2.7 Clinical Efficacy of Abdominal Functional Electrical Stimulation as a Neuro-Prosthesis

Currently, the most widespread use of AFES has been as a neuro-prosthesis. Previous work has determined the efficacy of this approach by assessing AFES-assisted pulmonary function tests, cough, and quiet breathing. In this section these clinical studies will be reviewed and discussed in relation to similar studies that have reported the use of other forms of neuro-prosthesis.

2.7.1 Standard Pulmonary Function Tests

There have been two studies that have investigated the acute effects of AFES using the FVC test [85, 159]. Zupan et al. found, in a group of thirteen tetraplegic patients with an injury level between C4 and C7, that unassisted FVC and FEV_1

were increased by 10%-20% when the patients were assisted by AFES [159]. The statistical significance of this result was not reported. In the second study, Langbein et al [85] investigated the effect of AFES in a study of ten SCI patients with injury levels ranging from C5 - T7. They found the group mean AFES-assisted FVC, FEV_1 and PEF to be to be 3.49 L, 2.73 L, and 6.24 L/s which showed a statistically significant increase over unassisted FVC, FEV_1 and PEF, of 3.08 L, 2.47 L, and 5.43 L/s respectively.

There have been comparably few studies which have reported AFES-assisted MEP. In a single case study, Lee et al. found AFES-assisted MEP to be 10 cmH_2O, which was greater than the patient's unassisted MEP of 6 cmH_2O [87]. In another study of eleven C3-T6 SCI patients, Butler et al. [24] found that gastric and oesophageal pressure showed a significantly increase during AFES-assisted MEP efforts compared with unassisted MEP efforts.

To date, there has been one study which has investigated whether abdominal muscle reconditioning improves the effectiveness of AFES to augment unassisted pulmonary function measures [159]. In the first study, thirteen tetraplegic subjects completed a four week intervention of expiratory muscle training which included breathing exercises complemented with AFES. The results showed a statistically significant increase in AFES-assisted FVC and FEV_1 over the course of the intervention. However, since unassisted FVC and FEV_1 also increased and the study did not provide numerical data, it is not clear whether AFES-assisted outcome measures increased relative to, or in parallel to, the unassisted outcome measures.

Functional Magnetic Stimulation and Spinal Cord Stimulation Assisted Pulmonary Function Tests

To the author's knowledge there have been no studies which have investigated the acute effects of FMS or SCS using standard FVC and MEP manoeuvres. Lin et al. [92] measured the effect of FMS on unassisted MEP and PEF from FRC. As shown in Table 2.4 (Section 2.7.2), FMS-assisted PEF from FRC, was significantly greater than unassisted PEF from FRC. In addition, the FMS-assisted MEP from FRC of 66.4 cmH_2O was significantly greater than unassisted MEP from FRC of 56.2 cmH_2O.

Discussion

It is difficult to make direct comparisons between the studies described above as a result of the different measurement methodology. This difficulty is compounded

by the heterogenous case mix of patients who participated in each study. One reasonable point of comparison is the improvement in unassisted PEF when FMS and AFES are used acutely. Lin et al. [92] reported an 11% increase in PEF when using FMS, versus a 15% increase reported by Langbein et al. when using AFES [85]. However, it should be noted that the two studies measured PEF from different lung volumes. From these limited studies it would appear that the two technologies yield similar results.

The outcome measures from the FVC and MEP test are important as they can give a general indication of health of the respiratory system. In particular, PEF measured during an FVC manoeuvre has been shown to be comparable to the PEF during cough [20]. Although these tests are useful indicators it is also important to gain an understanding of how respiratory neuro-prosthesis affects functional respiratory outcome measures. The subsequent sections will review the effect of respiratory neuro-prosthesis on cough and quiet breathing.

2.7.2 Cough

The first application of AFES in patients with tetraplegia was as a method of improving cough. This application was originally investigated in 1993 by Linder et al. [93] and Jaeger et al. [75]. These authors found a statistically significant increase in MEP [93] and CPF [75] between unassisted and AFES-assisted cough. This result has been corroborated by several other studies (see Table 2.4) [24, 24, 57, 58, 89, 140].

Taylor et al. [140] reported the greatest difference between AFES-assisted CPF (7.1 L/s) and unassisted CPF (4.6 L/s). This was achieved in a case study covering only a single patient which restricts the generalisation of this result. Butler et al. [24] have had the greatest success in augmenting unassisted cough using AFES in a group of eleven subjects. They found the mean AFES-assisted CPF to be 4 L/s, which was 35% greater than the mean unassisted CPF. To date, there has been only one study that has not found a statistically significant difference between AFES-assisted cough and unassisted cough [133].

There have been two studies that have investigated the effect of a period of abdominal muscle reconditioning on AFES-assisted cough [87, 104]. In the single case study [87], the patient participated in cough training sessions, in which he was asked to practice AFES-assisted coughing, 20-30 minutes per day for four weeks. The results showed that unassisted CPF increased from 3 L/s to 3.8 L/s, and that AFES-assisted CPF increased from 3.3 L/s to 5 L/s. The second study, which was published after the clinical experiments of this thesis were finished, was

a randomised crossover trial which included fifteen SCI patients who completed fifty AFES-assisted coughs per day, five days per week, for six weeks. The results showed that AFES-assisted CPF increased from 3.1 to 3.6 L/s [104].

There have been two case studies which have reported chronic use of an AFES-assisted cough system for management of secretions [87, 140].

Functional Magnetic Stimulation Assisted Cough

FMS was first proposed as a technology to assist with cough by Lin et al. [91] in 1998. Lin et al. [91] initially tested the feasibility of using FMS for cough assistance in a study of twelve able-bodied subjects and found that the PEF generated from FMS was not significantly different from the PEF that subjects could generate voluntarily. This result was later confirmed by Polskey et al. [121]. Subsequently, Lin et al. [92] investigated the effect of FMS in a cohort of tetraplegic patients where they found that FMS-assisted PEF was significantly greater than unassisted PEF (see Table 2.4).

Spinal Cord Stimulation Assisted Cough

DiMarco et al. have been the only group to research the use of SCS to improve cough in tetraplegia. In the seminal case study [39], SCS was able to increase unassisted PEF (measured from total lung capacity) from 2.4L/s to 7.2L/s. In addition, SCS allowed the patient to become completely independent of caregiver assistance for airway management. DiMarco et al. succeeded this case study with a clinical trial involving nine tetraplegic patients [40, 41]. The clinical trial showed that SCS significantly improved unassisted PEF from 1.86L/s to 8.8L/s and, in addition, compared with the period pre-implant, significantly reduced the number of respiratory infections and level of caregiver report. It should be noted that in both of the studies by DiMarco et al. [40, 41] the subjects received a period of muscle reconditioning (lastings six weeks in the case study [39] and for an unspecified time before the start of the clinical trial [40, 41]).

Discussion

The studies described above have shown that either AFES, FMS, or SCS can be used acutely to increase unassisted CPF. From these studies it is clear that SCS is the most efficacious in improving unassisted CPF when compared with either AFES or FMS. The reports of FMS-assisted cough suggest it is more effective at improving CPF than AFES. However, it should be noted that the

Table 2.4: The effect of respiratory neuro-prosthesis on CPF reported in previous studies. All measurements of CPF were made during a cough effort while patients were seated, unless otherwise stated. PI: time post injury.

Author	Type	N	Demographics	Unassisted PEF (L/s)	Assisted PEF (L/s)
Jaegar et al [75]	AFES	14	Injury level: C4-C7, AIS: A-D, PI: 1-86 months	3.38	3.83 *†
Taylor et al. [140]	AFES	1	Injury level: C3, AIS: -, PI: -	4.6	7.1
Gollee et al. [57]	AFES	4	Injury level: C4-C6, AIS: A-B, PI: 3 months - 5 yrs	1.93	2.73
Spivak et al. [133]	AFES	10	Injury level: C4-C7, AIS: A-B, PI: 1-384 months	3.5	3.6 †
Gollee et al. [58]	AFES	4	Injury level: C4-C6, AIS: A-B, PI:3-60 months	-	Δ0.3
Lee et al. [87]	AFES	1	Injury level: C4, AIS: C, PI: 8 months	3	3.3 ‡
Butler et al. [24]	AFES	11	Injury level: C3-T6, AIS: A-C, PI: 0.3-43.4 yrs	2.95	4 *‡
McBain et al. [104]	AFES	15	Injury level: C4-T5, AIS: A-C, PI: 0.3 - 41.1 yrs	2.1	3.1 *‡
Lin et al. [91]	FMS	12	Able-bodied	5.3	4.8 §
Lin et al. [92]	FMS	11	Injury level: C4-C7, AIS: A-D, PI: 1-33yrs	4.73	5.28 *§
DiMarco et al. [39]	SCS	1	Injury level: C5/6, AIS: C, PI: 7yrs	2.4	7.2 ‡
DiMarco et al. [40]	SCS	9	Injury level: C3-C6, AIS: -, PI: 1-34yrs	1.86	8.8 *‡

* Indicates a statistically significant difference between group mean unassisted CPF and AFES-assisted CPF
† CPF measured while patient supine
‡ CPF measured from total lung capacity
§ CPF measured from end inhalation lung volume

unassisted PEF was considerably greater in the study by Lin et al. [92] than in most of the studies that have investigated AFES-assisted cough. This difference in baseline unassisted cough between the AFES and FMS studies in addition to other confounding factors such as measurement protocol, make a comparison of efficacy between the two technologies difficult.

As discussed in Section 2.3.5, since there is not a standard method of measuring cough, the measurement protocol used varies considerably between studies. In addition, different authors have used different electrode configurations and stimulation parameters. Despite these confounding factors, the author believes that using an optimised electrode configuration [88] and instructing patients to cough from total lung capacity, contributed to the success of the protocol used by Butler et al. [24] compared with previous researchers.

AFES-assisted CPF is smaller than SCS-assisted CPF. However, AFES-assisted coughing would be clinically useful if it produced a clinically significant cough of greater than 4.5 L/s (see Section 2.2.4). The study by Butler et al. [24] showed AFES-assisted CPF to be 4L/s, which is close to clinical significance. However, the subject cohort were all at least one year post injury, and thus likely to have considerable atrophy of the abdominal muscles [26, 51]. Given the results from the studies by Lee et al. [87] and McBain et al. [104], which showed an increase in AFES-assisted CPF following a period of cough training, and the findings reported in Section 2.7.1, which showed that abdominal muscle training could improve AFES-assisted PEF, it is possible that AFES-assisted cough might become clinically useful after a period of abdominal muscle training. Furthermore, the successful demonstration of this hypothesis would be consistent with the two AFES case studies presented in this section which both reported improved respiratory health and continued use after the conclusion of the study [87, 140]. If it can be shown that AFES-assisted cough is clinically useful then it would be a feasible alternative to SCS -assisted cough, without the risks associated with an implanted device.

2.7.3 Quiet Breathing

To date, AFES is the only type of neuro-prosthesis that has been investigated as a method of improving quiet breathing in patients with tetraplegia.

Sorli et al. [132] were the first to demonstrate that AFES could be used to increase V_T in a study of nine able-bodied subjects. This study showed that AFES applied in synchrony with volitional exhalation statistically significantly increased unassisted V_T from 667 ml to 1100 ml, BR from 16 breaths/min to

18.6 breaths/min, and $\dot{V}$ from 10.3 L/min to 17.5 L/min.

Stanic et al. [134] continued the work of Sorli et al. in a follow up study which included six healthy subjects and five tetraplegic patients (Injury level: C4-C7, AIS: -,PI: 18-42 yrs). In the healthy subjects, Stanic et al. confirmed the results of Sorli et al. and in the tetraplegic patients Stanic et al. found AFES produced a statistically significant increase in V_T from 629 ml to 852 ml and $\dot{V}$ from 9.7 L/min to 14.2 L/min. AFES also increased unassisted BR from 15.5 breaths/min to 17 breaths/min but the difference was not statistically significant.

Gollee et al. have published two papers on the use of AFES to assist with quiet breathing in tetraplegia [55,58]. Both of these papers confirmed that AFES could significantly improve unassisted V_T in tetraplegia. Gollee et al. [58] also confirmed that AFES could significantly improve unassisted $\dot{V}$ in tetraplegia. However, contrary to the results of Stanic et al. [134], Gollee et al. [58] found that AFES significantly reduced unassisted BR. Lastly Gollee et al. [58] found that ET_{CO_2} during AFES-assisted breathing was lower than ET_{CO_2} during unassisted breathing for some subjects.

Discussion

The findings presented in this section show that AFES can increase V_T, BR and thereby $\dot{V}$ (which is calculated from the product of V_T and BR). There are however several important unanswered questions.

The extent to which AFES-assisted breathing affects alveolar ventilation is unknown since the increase in $\dot{V}$ could also be affecting the ventilation to perfusion ratio (see Section 2.1.3.) The finding by Gollee et al. which showed a reduction in ET_{CO_2} during AFES-assisted breathing suggests only that alveolar ventilation is being increased [58].

The investigation by Gollee et al. [58] suggests that the increase in $\dot{V}$ during AFES-assisted breathing is sufficient to compensate for the increase in carbon dioxide which would be expected from the additional abdominal muscle contraction during AFES-assisted breathing. However, the study by Gollee et al. [58] included only four subjects and therefore further work is required to fully understand this aspect of AFES-assisted breathing.

The temporal effect of AFES on quiet breathing parameters has not been investigated. A limitation of the previous work is that the difference between unassisted and AFES-assisted breathing has been quantified as a single static measurement by comparing the means taken over a period of breathing. If ET_{CO_2}

is modified in response to AFES, this would indicate a change in respiratory drive, in which case the temporal response would become particularly interesting.

The possibility of improving the effectiveness of AFES-assisted breathing using muscle reconditioning has not previously been studied. As was discussed in Section 2.7.1, there is evidence that shows that a period of abdominal muscle training results in improvements in standard pulmonary indicators. Therefore, it is possible AFES applied chronically may alter the effect of AFES on quiet breathing.

2.8 Clinical Efficacy of Using Abdominal Functional Electrical Stimulation for Neuromuscular Training

The second AFES paradigm presented in Section 2.5.1 was respiratory neuromuscular training. To date, there have been two studies which have investigated a purely AFES neuromuscular training programme [87, 104]. In the first case study, the patient completed twenty to thirty minutes of AFES-assisted coughing per day for four weeks. The results of this study showed that unassisted CPF increased from 3 L/s to 3.8 L/s over the course of the study [87]. In the second study, fifteen patients completed approximately fifty AFES-assisted coughs per day over a period of six weeks. The results of this study showed that unassisted CPF increased from 2.1 L/s to 2.5 L/s over the training period, but the increase was not statistically significant.

There have been two other studies which, despite including elements in addition to AFES, demonstrate the feasibility of the AFES neuromuscular training [27, 159].

In the study by Zupan et al. [159], thirteen tetraplegic patients completed a four week intervention of expiratory muscle training, which included breathing exercises assisted with AFES (i.e. an active training programme). The results of this study found a significant increase in unassisted FVC and FEV_1 of 17% and 16% respectively when the patients were in the supine position. There was no change in unassisted FVC and FEV_1 when patients were in the seated position [159].

In the second study, Cheng et al. [27] conducted a randomised controlled trial on the effects of pectoral and abdominal neuromuscular training on the unassisted respiratory function of patients with tetraplegia. The training protocol used in

this intervention did not require active participation by the study subjects (passive neuromuscular training). In the treatment group of this trial, stimulation was applied for 30 mins/day, 5 days/week, for 4 weeks. At the end of the intervention:

- Unassisted FVC had increased from 1.71 L to 2.26 L (δ: 0.55 L, p < 0.01)

- Unassisted FEV_1 had increased from 1.78 L to 2 L (δ: 0.22, p < 0.01)

- Unassisted PEF had increased from 2.96 L/s to 3.93 L/s (δ: 0.97 L/s, p < 0.01)

- Unassisted maximum inspiratory pressure had increased from 39.5 cmH_2O to 49.2 cmH_2O (δ: 9.7 cmH_2O, p < 0.01)

- Unassisted MEP had increased from 30.8 cmH_2O to 39.8 cmH_2O (δ: 9 cmH_2O, p < 0.01)

No significant changes were found for the control group which did not receive any stimulation. In addition to investigating pulmonary function measures, Cheng et al. found that the frequency of respiratory complications in the 6 months following the start of the study were significantly lower in the intervention group than in the control group.

2.8.1 Functional Magnetic Stimulation Neuromuscular Training

As far as the author is aware the only study which has investigated the benefits of using FMS for neuromuscular training is that reported by Lin et al. in which they applied FMS to a group of eight tetraplegic patients (injury level: C4-T5, AIS: A-B, PI: 2-27 yrs) for 20 minutes/day, 5 days/week for four weeks [90]. Over the course of the intervention, MEP showed a significant increase from 22.9 to 29.6 cmH_2O. PEF did not change significantly. Two weeks after the conclusion of the study all pulmonary function measures had returned to their pre-training levels.

2.8.2 Discussion

The respiratory neuromuscular training studies that included AFES showed statistically significant increases in unassisted FVC, FEV_1 and PEF. However, it is difficult to interpret the contribution of AFES in these studies because the intervention also included other training modalities. In the case of Zupan et al. [159],

AFES was combined with breathing exercises. In the case of Cheng et al. [27], AFES was combined with FES of the pectoralis major muscles. The case study by Lee et al. [87] demonstrated that similar results could be expected in a purely AFES training programme. However, since it included only one patient, further work is required before conclusions can be drawn.

Although the increases in MEP following FMS [90] and FES neuromuscular training [27,87,159] were similar, there was no significant change in PEF following FMS training [90] whereas there was a moderate and significant change in PEF following FES neuromuscular training [27, 87, 159]. From the evidence available it appears that FES neuromuscular training is at least comparable, but possibly more effective, than FMS neuromuscular training.

The intervention studies presented in this section have demonstrated the feasibility of training the abdominal muscles to improve unassisted respiratory function in tetraplegia. In addition, the study by Cheng et al [27] indicated that there is a correlation between improvements in unassisted respiratory function and the frequency of respiratory complications.

2.9 Weaning From Mechanical Ventilation: A New Method of Using Abdominal Functional Electrical Stimulation?

The previous sections have focussed on the use of AFES in spontaneously breathing tetraplegic patients; either as an assistive device or as a respiratory rehabilitation tool. In this section, new approaches to weaning a patient from MV will be discussed and a novel method of using AFES will be presented.

As discussed in Section 1.2.1, the process of weaning a patient from a MV typically revolves around a weaning protocol (for example t-piece weaning). An emerging technique that may accelerate this process is the use of respiratory muscle training. Although using respiratory muscle training has not been tested in SCI patients it has been shown to be successful at reducing weaning time in non-SCI patients who required MV [101].

For patients who are unable to wean from MV, phrenic nerve stimulation is the most widely used alternative to mechanical ventilation. Phrenic nerve pacing is associated with a higher initial cost but also with a significant reduction in respiratory infections and an improved quality of speech [38]. The high initial

cost is offset with the associated benefits. One institution found that the pay-back period for the initial investment was less than one year when the reduced respiratory infections, reduced requirement for single use equipment, and reduced care-giver time were taken into account [71]. Patients whose phrenic nerves are damaged are not suitable candidates for phrenic nerve stimulation [38, 130]. For those patients diaphragm pacing using intramuscular electrodes [45] or combined intercostal and phrenic nerve pacing [43] may be considered as alternatives.

Another option for patients who are only partially dependent on MV is the pneumobelt. The pneumobelt is an inflatable corset which is worn around the abdomen and inflated and deflated by a positive pressure ventilator. The pneu-mobelt acts on the abdomen in a similar fashion to AFES and on average users can achieve 12 to 14 hours of ventilation. Since all the equipment required for the device can be contained on a wheelchair, the pneumobelt considerably improves mobility for patients. In addition, other reported advantages compared with a MV connected to a tracheostomy include improved cosmetic appearance, speech, comfort, safety and health [111].

There has been only one report of AFES used in ventilator dependent patients. In this case study, AFES was used to support breathing in tetraplegic patients with diaphragm paralysis [78]. Since the patients in this case study were unable to breathe spontaneously, AFES open-loop control was used to apply AFES at the same rate as the patient's normal ventilator settings. Using this technique, ventilator free breathing was supported for up to 210 s.

2.9.1 Discussion

Previous literature has demonstrated the feasibility of using AFES to support ventilator free breathing in patients who were otherwise MV-dependent. While the maximum duration of ventilator free breathing was short (210 s), it is pos-sible that this could be extended following a period of abdominal muscle recon-ditioning. However, it is unlikely that AFES could be developed into a practical alternative to MV. This is partly due to the inherent limitations of AFES, and partly because there are other well established alternatives to MV.

Due to the inherent risk of an implanted device (see Section 2.6.3), phrenic nerve pacing is less preferable to weaning from MV. However, aside from the established weaning guidelines there is a paucity of interventions that can be used to assist in this process. Respiratory muscle training has been shown to be useful in improving weaning outcomes in other patient groups and future research may also find that it can also be used to help with weaning in SCI.

As was discussed in Section 2.8, interventions that incorporate AFES have been shown to improve unassisted breathing volumes in tetraplegic patients who can breathe spontaneously. This finding, combined with the observation that respiratory muscle training has previously been used to assist patients wean from MV, raises the question: can AFES applied chronically be used as an intervention to assist SCI patients wean from MV?

Chapter 3

Study 1: Methods

AFES can either be used as a respiratory neuro-prosthesis or for respiratory neuromuscular training [5]. Previous research has shown that as a respiratory neuro-prosthesis and compared with a SCI person's unassisted respiratory effort, AFES can acutely augment standard respiratory indices (FVC, FEV_1, PEF and MEP, see Section 2.7.1), CPF (see Section 2.7.2), and V_T during quiet breathing (see Section 2.7.3). There have been no prior investigations on the impact of repeated regular use of AFES on AFES-assisted respiratory outcome measures. SCI is associated with considerable disuse atrophy of the skeletal muscles, including the abdominal muscles [51], and therefore it is possible that a period of abdominal muscle reconditioning would lead to improved AFES-assisted respiratory outcomes.

There is limited evidence emerging that respiratory muscle training, using either neuromuscular stimulation or breathing exercises, can lead to improved unassisted respiratory outcome measures (see Section 2.8). It is not known whether a training programme that uses AFES exclusively would be efficacious. Such a programme would have practical advantages which are an important consideration in a busy hospital.

Leading on from previous work the primary aims of this study were:

1. To determine the effect of AFES neuromuscular training on AFES-assisted breathing in tetraplegia.

2. To determine the effect of AFES neuromuscular training on unassisted breathing in tetraplegia.

This study also included two secondary aims:

1. To investigate the use of a CIT during AFES-assisted cough. CPF is dependent on the intrathoracic pressure generated during the glottal closure

and expulsive phases of coughing. Contraction of the abdominal muscles contributes to this pressure. Therefore the more forceful the contraction of the abdominal muscles, the greater the increase in intrathoracic pressure and CPF. It is known that a CIT can increase the force production in electrically stimulated muscle compared with a CFT, though it has not been used in the application of AFES-assisted cough.

2. To characterise the temporal response of ventilatory and blood-gas measurements during extended periods of AFES-assisted breathing. Gollee et al. [58] previously observed a decrease in ET_{CO_2} during AFES-assisted breathing in a limited number of tetraplegic patients. They postulated that the increased ventilation induced by AFES offset the increase in metabolic demand resulting from contraction of the abdominal muscles. This observation needs to be verified in a larger patient group. In addition, in all previous studies the effect of AFES on quiet breathing has been determined by comparing mean ventilatory parameters between unassisted and AFES-assisted breathing. It is possible that the effect of AFES on ventilation would change over time and therefore this aspect needs to be investigated.

To address the aims of this study, tetraplegic patients who could breathe spontaneously were invited to participate in a three week AFES training programme. Throughout the programme, the patients' unassisted and AFES-assisted respiratory functions were measured using a combination of standard breathing tests and continuous breathing tests. The standard breathing tests included the FVC test and the MEP test; the continuous breathing tests included a cough assessment and a quiet breathing assessment.

This chapter describes the equipment, study design, training protocol, testing methods and general analysis methods used. This chapter also details the subjects who participated in this study and describes deviations from the defined protocol.

Chapters 4 to 6 present the results of individual breathing tests and discuss their implications.

3.1 Subjects

This study aimed to recruit tetraplegic subjects based on the following inclusion and exclusion criteria.

The inclusion criteria for the study were:

- tetraplegia following spinal cord injury (AIS A-C)

- and no useful abdominal movement

- and able to breathe without the use of artificial ventilation

- and reduced vital capacity

- and visual contraction of the abdominal muscles in response to AFES.

The exclusion criteria were:

- pregnancy

- or a significant history of autonomic dysreflexia

- or unable to give informed consent

- or under the age of 16.

A sample size calculation was performed for this study as the quantitative effectiveness of the AFES intervention was unknown. Instead, in this exploratory study, the number of subjects recruited was determined by the available eligible patient population during the study time. All procedures were approved by the NHS Greater Glasgow and Clyde Local Research Ethics Committee. All subjects gave written informed consent.

3.2 Equipment and Setup

Figure 3.1 shows a picture of the equipment that was used for the study.

Figure 3.1: Apparatus

Table 3.1: Output charactersitics of the RehaStim. * Maximum frequency range when using four stimulation channels.

Parameter	Output range
Current	0 mA - 126 mA
Pulsewidth	20 μs - 500 μs
Frequency*	0 Hz - 222 Hz

3.2.1 FES Stimulator

A stimulator (RehaStim, Hasomed, Germany) was used to apply bi-phasic, charge balanced, transcutaneous FES to the abdominal wall muscles. The output ranges of the stimulation parameters for the stimulator are given in Table 3.1. Stimulation was delivered across four channels using eight surface electrodes (3.3 cm x 5.3 cm and 5 cm x 9 cm, PALS Platinum, Nidd Valley Medical, UK). Generally the larger electrodes were used for stimulation channels one and four, while the smaller electrodes were used for channels two and three. Electrodes were placed over the rectus abdominis and external oblique muscles as shown in Figure 3.2.
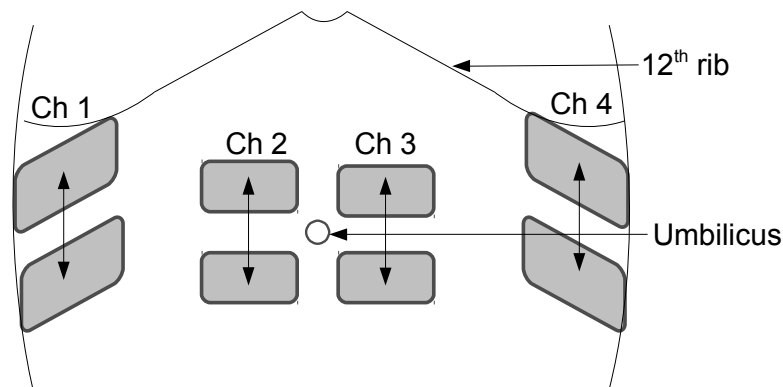
Figure 3.2: Electrode placement. Pairs of electrodes that make up single stimulation channel are illustrated with the double-headed arrows. Each stimulation channel is indicated with the 'Ch' prefix.

In the assessment sessions (Section 3.5), the stimulator was controlled by an external PC ('Science-Mode') using custom designed software described in this section. In the AFES training sessions (Section 3.6), the stimulator was controlled using its on-board programme.

In 'Science-Mode' the timing of individual stimulation pulses was controlled by the stimulator's on-board microcontroller while an external PC turned stimulation on and off and controlled the stimulation parameters (current, frequency, pulse width, and pulse pattern, see Figure 2.4 on page 27). The two types of

pulse pattern used in this thesis[1] were single pulses and doublets. The single pulse pattern delivered stimulation pulses at the main stimulation frequency. In comparison, the doublet pulse pattern delivered groups of two single pulses at the main stimulation frequency while individual pulses within the group were spaced according to a separate (greater) frequency.

The on-board stimulator programme applied a cyclic stimulation pattern which allowed stimulation to be applied in phase with a patient's volitional exhalation. The stimulation pattern consisted of a period of no stimulation followed by a period of stimulation. At the start of each training session the period of no stimulation was adjusted to correspond to the patient's inhalation time and the period of stimulation was adjusted to correspond with the patient's exhalation time. When using the on-board programme the stimulation current could be set for individual stimulation channels while the stimulation pulse width and frequency were equal for each stimulation channel. Throughout the training session the period of no stimulation and the period of stimulation were adjusted periodically to account for variations in breathing pattern. In addition, the stimulation pulse width was adjusted periodically to account for abdominal muscle fatigue.

3.2.2 Spirometer

Air flow rate and volume measurements were made using a hand held spirometer (Microloop, Micromedical, UK) connected to a low dead space full face mask (Hans Rudolph, USA).

The spirometer's on-board software was used to record the FVC test described in Section 3.5.1). After each FVC manoeuvre the software reported FVC, FEV_1 and PEF. In addition, the variation between successive FVC manoeuvres was reported as the percentage difference between the sum of the FVC and the FEV_1 from the best and the worst attempt.

The spirometer was used in 'live mode' with the assessment control system described in Section 3.3 to perform the continuous breathing tests described in Section 3.5.2. In this mode the total volume of air inhaled and exhaled since the start of recording (spiro_V) and the direction of air flow (spiro_D) was streamed in real-time to an external PC over a serial connection. From these two variables, breath-by-breath volume and flow rate could be calculated as described in Section 3.7.

---

[1]The stimulator was also capable of delivering a triplet pulse pattern

3.2.3 Mouth Pressure Meter

A mouth pressure measuring device (MPM, Micromedical, UK) was used to measure MEP at the mouth. Measurements were taken from total lung capacity using a flanged mouthpiece. The meter averaged the pressure over two second windows and reported the maximum average pressure.

3.2.4 Carbon Dioxide Monitor

ET_{CO_2} was measured using a carbon dioxide monitor (Datex Normcap, Intrumentarium, Finland) with its sampling line inserted into the tube which connected the spirometer and the facemask. The monitor included an analog display and an analog output of continuous partial pressure of carbon dioxide data. Consistent with the manufacturers instructions, the monitor was switched on at least five minutes before testing began to allow the reading to settle.

3.3 Stimulation System

A stimulation system was developed to apply AFES automatically in synchrony with a patient's volitional respiratory effort.

3.3.1 Hardware

A block diagram of the system is shown in Figure 3.3. The spirometer was used in 'live mode' and connected to the laptop PC via an RS232 serial connection. The carbon dioxide monitor, a potentiometer and a push button switch (both used to control the stimulation output) were interfaced to the laptop PC via a data acquisition card (NI USB-6009, National Instruments Corporation, Austin, Texas, USA). Finally, the stimulator was used in 'Science Mode' and interfaced to the laptop PC using a USB interface.

3.3.2 Graphical User Interface

A Graphical User Interface (GUI) (Figure 3.4) was designed using LabVIEW (National Instruments, Austin, Texas, USA) and interfaced to the control system implemented in Simulink (MathWorks, Massachusetts, USA) (described below) using the Simulation Interface Toolkit (National Instruments). The GUI allowed the researcher to switch between stimulation modes, adjust the stimulation current for each channel, view the stimulation pulse width (set by the potentiometer),
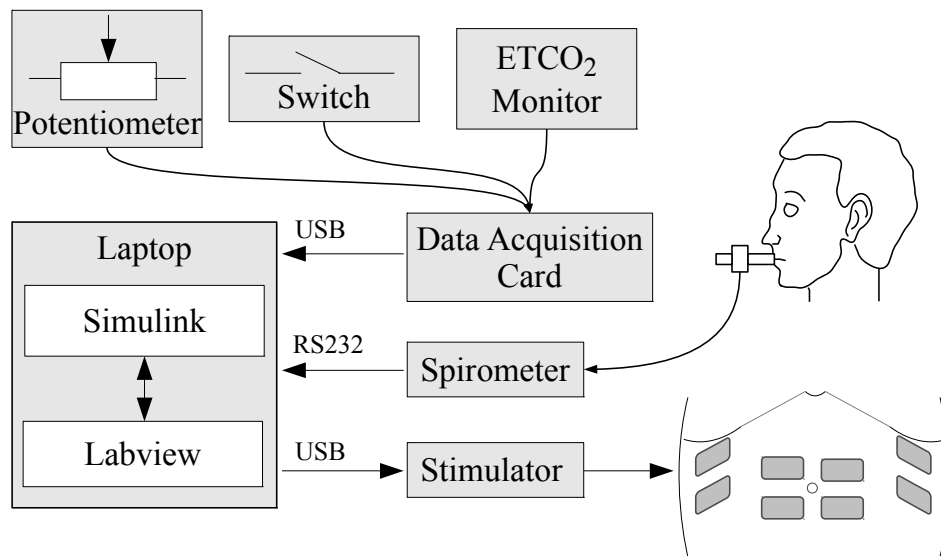
Figure 3.3: Block diagram of the system

and set the control algorithm parameters (described below). In addition, the GUI displayed continuous traces of breathing volume, average air flow rate and ET_{CO2}. The stimulation trigger output was superimposed onto the volume and flow rate displays to allow the researcher to monitor the stimulation timing and vary the parameters accordingly.
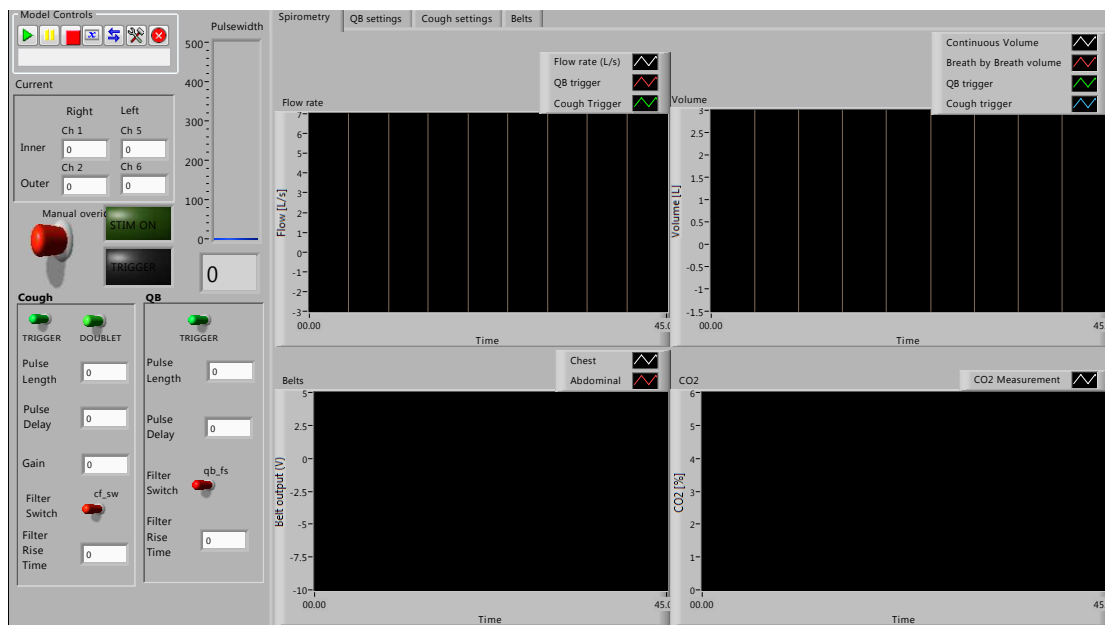
Figure 3.4: The GUI designed for the assessment control system

3.3.3 Control System

The system was controlled using software written in Simulink. Figure 3.5 is a flow chart of the overall system, which looped every 20 ms. At the start of the loop, the output of the spirometer, the carbon dioxide monitor, the potentiometer, the push button switch and the software inputs from the GUI were read. The spirometer outputs, Spiro_D and Spiro_V, were used to determine flow rate and the derivative of flow rate as shown by the flow chart in Figure 3.6. After the system inputs had been read, a stimulation trigger was generated by one of three modes: manual mode, cough mode, and quiet breathing mode (described below). The stimulation trigger was multiplied by the output of the potentiometer to give the value of the stimulation pulse width. The stimulation pulse width, in addition to the stimulation current for each channel (controlled by the GUI) was used to control the output of the stimulator. After the stimulator output had been adjusted the GUI was updated with the current status of the system. Finally, the current output of the spirometer, carbon dioxide monitor and stimulator and the status of each of the stimulation triggers were written to disk.
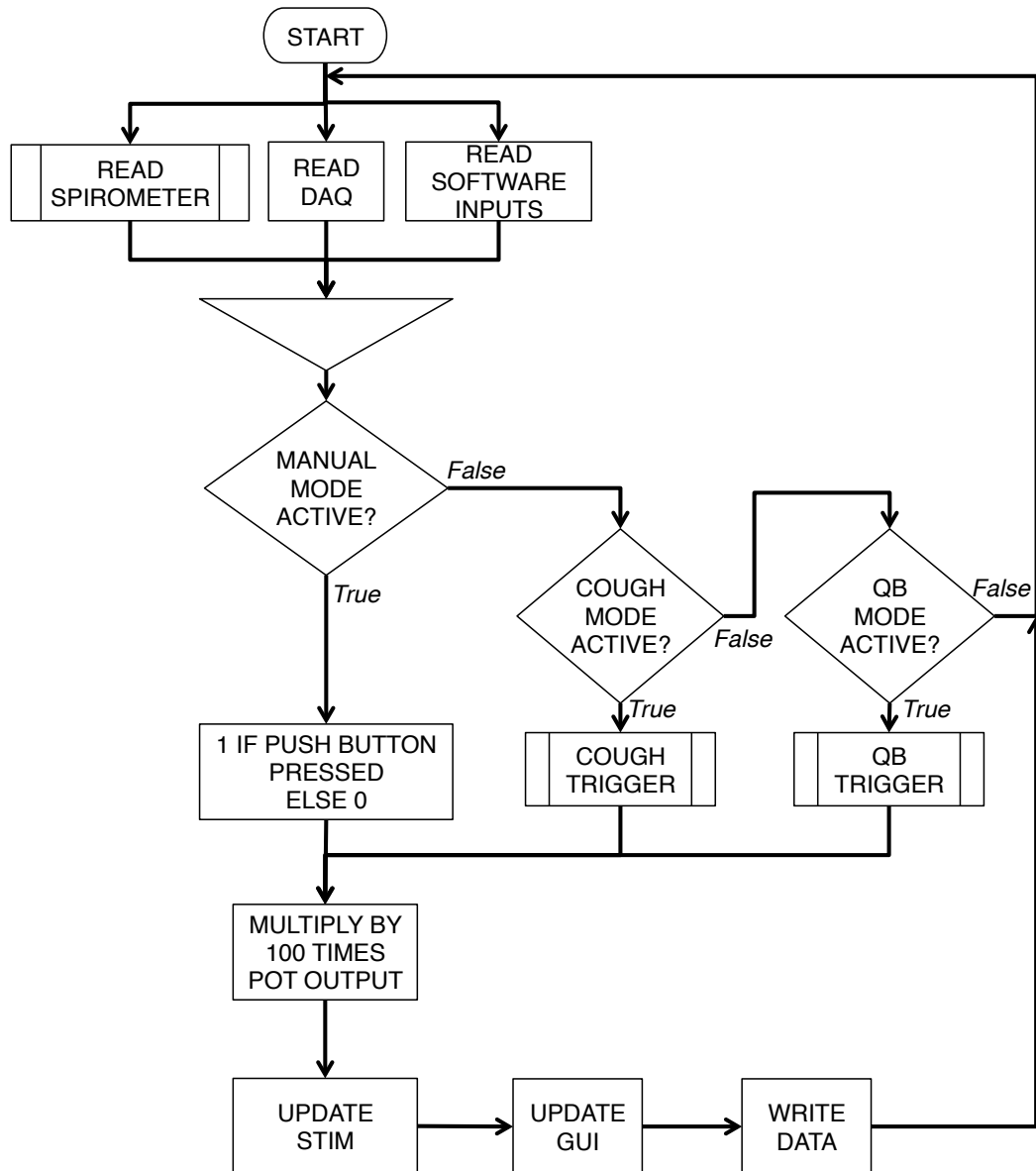
Figure 3.5: Flow chart of the overall control system control algorithm.

```
                        ┌──────────────┐
                        │    START     │
                        └──────────────┘
              ┌──────────────┘      └──────────────┐
         ┌─────────┐                          ┌─────────┐
        /  Sprio_V  /                         /  Sprio_D  /
       └──────────┘                          └──────────┘
    ┌──────────────┐                    ┌──────────────────┐
    │  DIFFERENCE  │                    │ 1 for Spiro_D ≥ 0 │
    │  FROM LAST   │                    │ -1 for Spiro_D < 0│
    │   SAMPLE     │                    └──────────────────┘
    └──────────────┘
              └──────────────┐      ┌──────────────┘
                        ┌──────────────┐
                        │  MULTIPLY    │
                        └──────────────┘
                        ┌──────────────┐
                        │ 10 TAP MOVING│
                        │AVERAGE FILTER│
                        └──────────────┘
                           /  Flow  /
                        ┌──────────────┐
                        │CHANGE IN FLOW│
                        │FROM PREVIOUS │
                        │SAMPLE (dFLOW)│
                        └──────────────┘
                        ┌──────────────┐
                        │ 10 TAP MOVING│
                        │AVERAGE FILTER│
                        └──────────────┘
                          /  dFlow  /
                        ┌──────────────┐
                        │     END      │
                        └──────────────┘
```
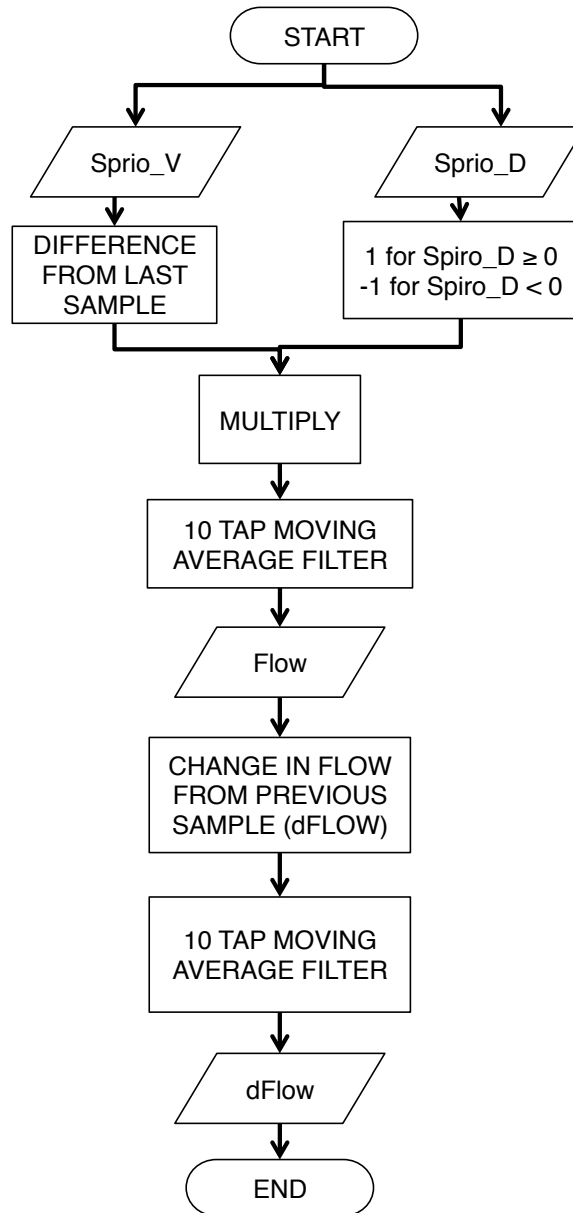
Figure 3.6: Flow chart of the spirometer subsystem

Manual Mode

In manual mode all automatic triggers were ignored and stimulation was turned on whenever the push-button switch was pressed. Stimulation was applied using a 30 Hz CFT and a stimulation current and pulse width that was adjusted on an individual subject basis (see Section 3.5).

Cough Mode

The cough mode used the cough algorithm as presented by Gollee et al. [57]. The goal of this mode was to distinguish between a normal breath and an attempt to cough, and to apply stimulation at the end of inspiration to coincide with the glottal closure phase of a cough.

A flow diagram of the cough mode algorithm is shown in Figure 3.7 and Figure 3.8 illustrates the stimulation output generated by the cough mode. When cough mode was active an attempt to cough was registered if the flow rate during inspiration crossed a negative threshold τ_{cflow}. Figure 3.8(a) illustrates the flow rate (solid line) during two example coughing cycles. In the figure, a negative flow rate corresponds to inhalation and the threshold τ_{cflow} is depicted by the dashed line. Since the peak inspiratory flow during a cough is normally greater than during quiet breathing, adjustment of τ_{cflow} allowed the algorithm to make a clear distinction between a quiet breath and a cough. Adjustment of τ_{cflow} was done on an individual subject basis.

The end of inspiration was taken as the point in which the flow rate started to increase during the inspiratory phase of the cough and determined as the point in which the derivative of flow rate during inhalation crossed a positive threshold τ_{cdflow}. Figure 3.8(b) illustrates the derivative of flow rate (solid line) during the example cough cycles shown in Figure 3.8(a) and the threshold τ_{cdflow} (dashed line). Adjustment of τ_{cdflow} was done on an individual subject basis to synchronise the start of stimulation with the glottal closure phase of the cough. Once an attempt to cough had been registered and the start of inhalation had been detected, the algorithm applied a stimulation burst of duration τ_{cstim}. τ_{cstim} was set to one second for all subjects and the stimulation burst is illustrated in Figures 3.8(a) and 3.8(b) by the shaded regions. If the direction of flow rate changed during the stimulation burst, indicating the start of inhalation, then stimulation was immediately turned off. As a safety precaution, the push button switch had to remain depressed for stimulation to be turned on.

In this mode stimulation could be applied using either a CFT or a CIT (determined through the GUI). The CFT was delivered at 30 Hz while the CIT
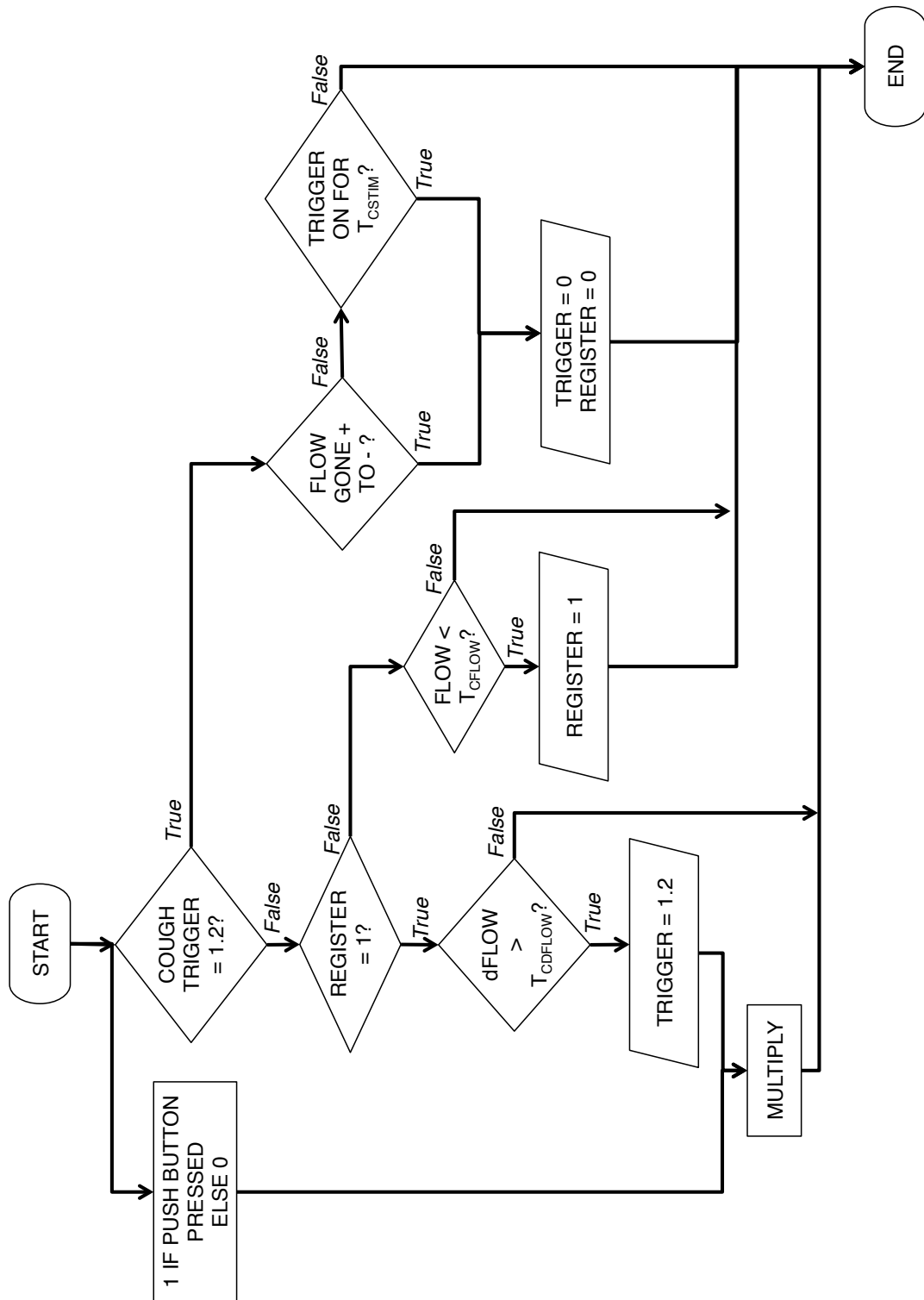
Figure 3.7: Flow chart of the cough trigger subsystem

included an initial doublet, delivered at 150 Hz, followed by a CFT delivered at 30 Hz. The stimulation current and pulse width were adjusted on an individual subject basis (see Section 3.5). Stimulation pulse width was filtered using a second order transfer function with a rise time of 0.1 s.

(a)

(b)
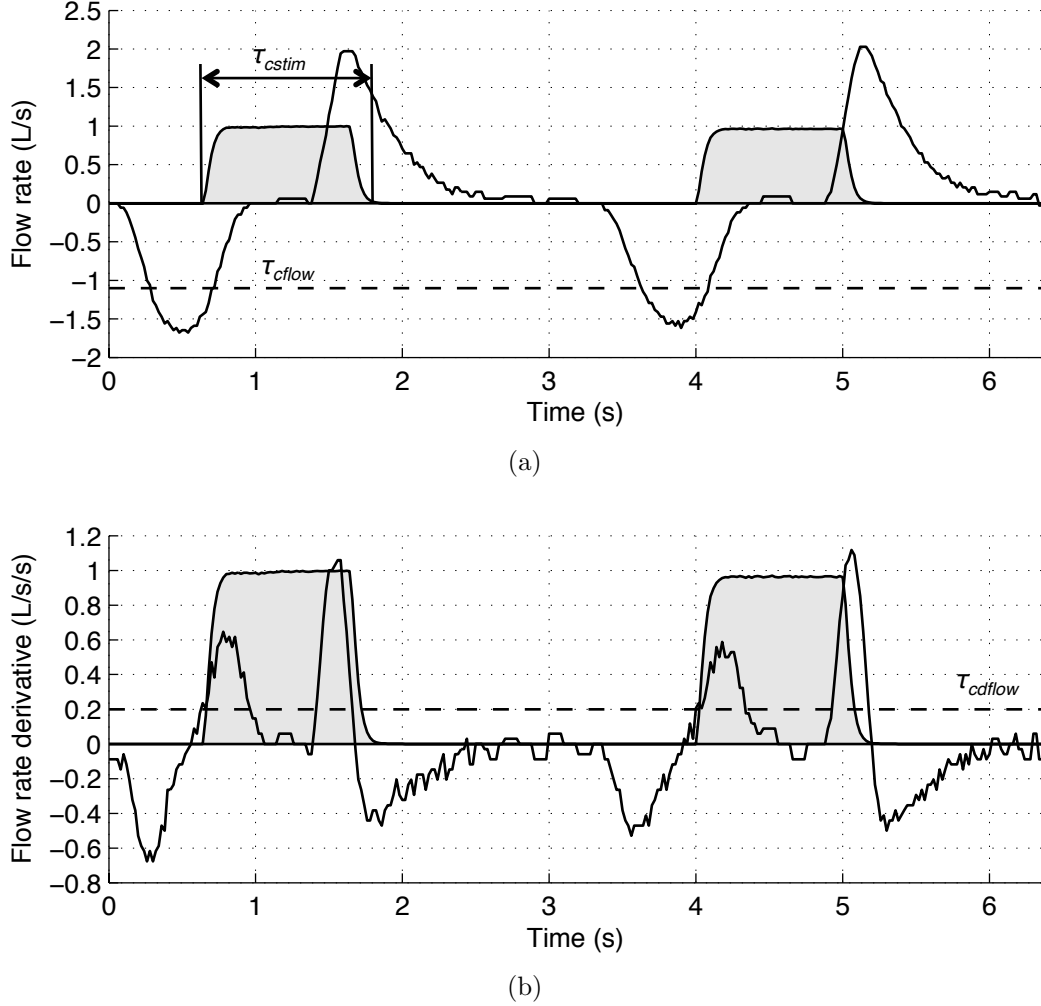
Figure 3.8: Illustration of the cough stimulation trigger. (a) An attempt to cough was registered when inspiratory flow crossed τ_{cflow}. (b) When the derivative of flow crossed τ_{cdflow} the cough stimulation burst (shaded area) was applied for τ_{cstim} seconds. Algorithm parameters were empirically determined for individual subjects.

Quiet Breathing Mode

The quiet breathing mode was based on the algorithm presented by Gollee et al. [57], but simplified to exclude the cross-correlation with a reference breath. A flow chart of the algorithm is shown in Figure 3.9. In this mode, stimulation was turned on for one second every time the direction of air flow ($spiro_D$) changed from negative to positive (the start of exhalation) as illustrated in Figure 3.10.

If the direction of airflow changed (indicating inhalation) during the stimulation period, stimulation was turned off. As a safety precaution, the push button switch had to remain depressed for stimulation to be turned on.

In this mode, stimulation was applied using a 30 Hz CFT and a stimulation current and pulse width that was adjusted on an individual subject basis (see Section 3.5). Stimulation pulse width was filtered using a second order transfer function with a rise time of 0.1 s.
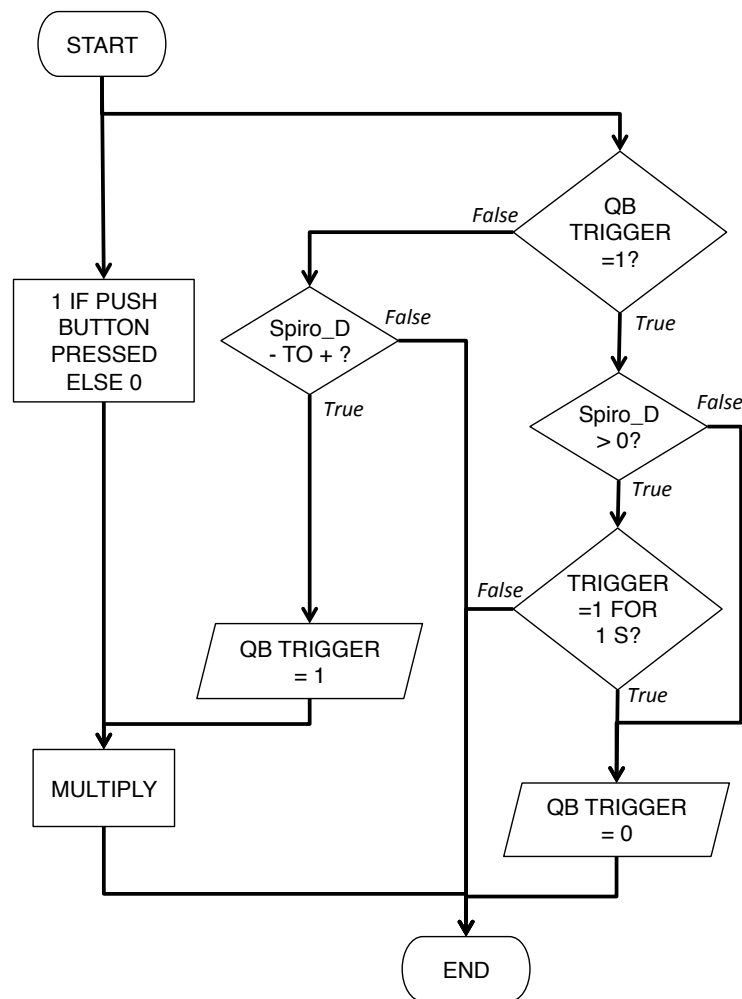
Figure 3.9: Flow chart of the quiet breathing trigger subsystem
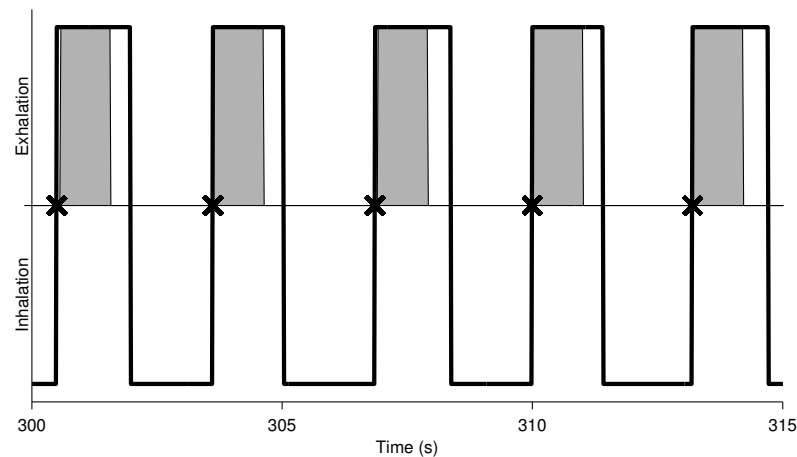
Figure 3.10: Illustration of the QB trigger. The black line is the $spiro_D$ signal from the spirometer and the crosses mark the beginning of exhalation. Stimulation (shown by the grey areas) was applied for one second at the onset of exhalation in the QB mode.

3.3.4   System Calibration and Validation

The manufacturer instructions for the spirometer state that the device does not need to be periodically calibrated. The calibration of the spirometer was verified by recording the volume output of the spirometer during five strokes of a 3 litre calibration syringe. To ensure that the system functioned correctly several trial runs of the study protocol were completed before formal data collection began.

3.4   Study Design

An outline of the study design is shown in Figure 3.11. The study consisted of three phases:

1. Control phase. This began at the start of the study and lasted for one week. The purpose of this phase was to determine whether the patients respiratory function was stable before the start of the training intervention.

2. Training phase. This began at the start of week two and lasted for three weeks. During this phase subjects participated in an incremental training program of AFES as described in Section 3.6 (page 70).

3. Follow up phase. This began at the beginning of week five and lasted for three weeks. The purpose of this phase was to assess whether the impact of training was sustained following its cessation.

Phase		Control		Training			Follow up		
Week		1	2	3	4	5	6	7	
Training (min/day)			20	40	60				
Assessment	A1	A2	A3	A4	A5				A6
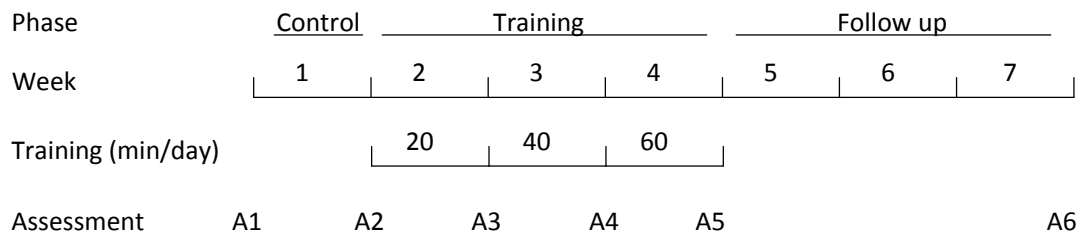
Figure 3.11: Outline of the study design

To monitor respiratory function through the study, each subject was asked to participate in six assessment sessions (A1 - A6) during which unassisted and AFES-assisted respiratory assessments were carried out as described in Section 3.5.

3.4.1 Initial Screening

At the beginning of the first assessment session each patient participated in a screening session. The screening session had two objectives.

1. To ensure that AFES did not cause a patient to become dysreflexic.
   It has been shown that because FES stimulates the sensory nerves as well as the motor nerves, it can trigger autonomic dysreflexia in some patients [7]. To assess this possibility, a physician monitored the patient for visible symptoms of autonomic dysreflexia and monitored the patient's blood pressure while quiet breathing stimulation was applied for approximately two minutes.

2. To determine whether a patient's abdominal muscles responded to AFES. In some cases of SCI there is lower motor neuron damage in addition to upper motor neuron damage. If the lower motor neuron damage affected the intercostal nerves that supply the abdominal muscles, AFES would not cause the abdominal muscles to contract. This objective was assessed by ensuring that a visible muscle contraction was present bi-laterally in the rectus abdominis and external oblique muscles in response to AFES.

3.4.2 Dealing with Illness and Bed Rest

The main interruptions to the study protocol resulted from illness or periods of bed rest used to treat pressure sores. These were dealt with as follows:

- If an illness lasted from one to three days, the study protocol was resumed from the training or assessment session missed.

- If an illness lasted for more than three days but less than one week, then one or two training sessions were added to the protocol before the next assessment session.

- If an illness lasted for more than one week during the training phase the patient was removed from the study. A delay of up to two weeks was deemed acceptable during the control or follow up phases of the study.

- If a patient was being treated with bed rest the training sessions continued. Assessment sessions were not conducted during bed rest since patients were required to be sitting in their wheelchair.

- If the bed rest coincided with assessment sessions A3 or A4 these were skipped, for other assessments the same policy as that outlined for illness was used.

3.4.3   Changes to the Training and Assessment Protocols

The training and assessment protocols were modified (refer to the respective sections for details of the protocols used) after subjects S1, S2 and S3 had completed the study. The protocols were changed to improve the consistency of both the AFES application and the standard clinical tests.

3.5   Assessment Protocols

Assessment sessions always took place while patients were seated in their wheelchair since it is known that lung volumes vary significantly between a sitting and a supine posture [95]. Each assessment session started by placing the electrodes over the subjects abdomen and connecting them to the stimulator. The stimulation frequency was set at 30 Hz for all tests (except the CIT cough test), this frequency was chosen to match the stimulation frequency during the training sessions (see Section 3.6). The current for each channel of stimulation was adjusted until a strong visible contraction of the corresponding muscle group was observed at a constant pulse width of 150 μs. Following this, stimulation to all channels was applied simultaneously. Adjustments were then made to the current settings for each channel until an even contraction across the abdomen was obtained. To ensure maximum muscle contraction the pulse width was increased during the AFES-assisted MEP tests until no further gains in MEP were achieved. Adjusting the stimulation current and pulse width to give maximum muscle contraction

was done to improve the repeatability of the stimulation setup. The contraction of the abdominal muscles were visually monitored throughout the assessment session for fatigue. If the contraction appeared to weaken then the stimulation pulse width was increased to compensate.

The standard clinical respiratory tests and continuous breathing tests proceeded according to the time-line shown in Figure 3.12.

MEP test
    1) Unassisted attempts
    2) AFES-assisted attempts

FVC test
    1) Unassisted attempts
    2) AFES-assisted attempts

— Standard clinical tests

Cough test
    1) 5 to 6 unassisted coughs
    2) 5 to 6 CFT coughs
    3) 5 to 6 CIT coughs (initial doublet)

QB test
    1) 1 minute unassisted QB
    2) 5 minutes AFES-assisted QB
    3) 1 minute unassisted QB

— Continuous breathing tests
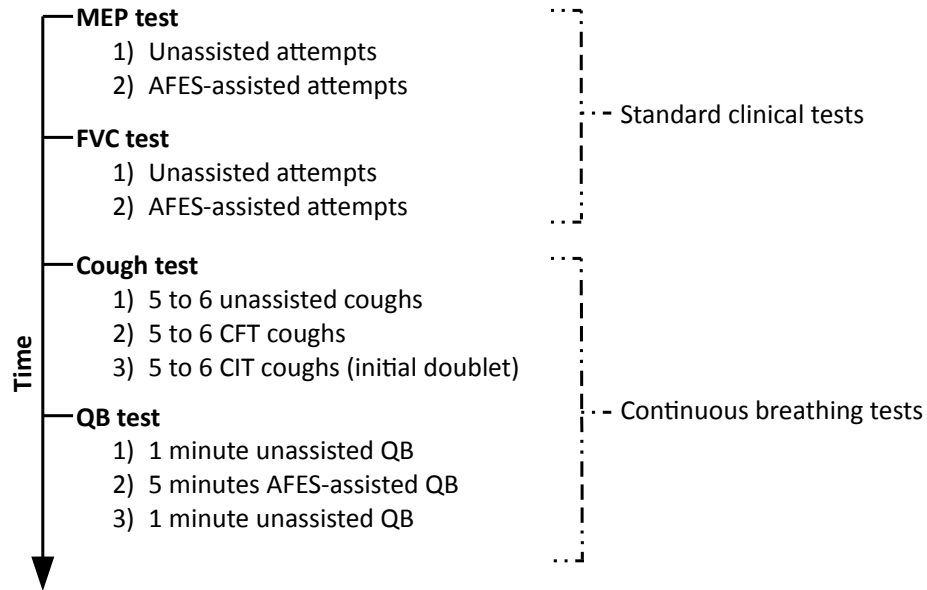
Time

Figure 3.12: Time line for assessment session tests

3.5.1 Standard Clinical Respiratory Tests

Two standard clinical respiratory tests were performed in each assessment session: the MEP test and the FVC test (see Section 2.2 for a description of these tests). In both of these tests, the researcher triggered AFES manually so that stimulation coincided with the beginning and end of exhalation. Subjects were asked to attempt each test up to five times, or until three valid attempts had been collected (see below). Tests and control of AFES were conducted by the same researcher in every assessment session.

Maximum Expiratory Pressure Test

The 'expiratory' one-way valve was fitted to the mouth pressure meter. This allowed the subject to inhale through the mouthpiece without affecting the meter. Subjects were instructed to place the flanged mouthpiece under their lips and

to put the bite blocks of the mouthpiece between their teeth. They were then instructed to inhale to total lung capacity before exhaling as forcefully as possible for at least two seconds. Subjects were told not to use the muscles of their cheek to help generate pressure and were encouraged throughout the manoeuvre. Three valid attempts were counted when the MEPs were within 20% of each other.

Forced Vital Capacity Test

The facemask was secured using a net which was placed around the back of the subject's head and clipped on to both sides of the facemask. The net was tightened to ensure that there were no air leaks from the mask. A cardboard connector tube was used to connect the spirometer to the mask and the spirometer was set to 'FVC' test mode. Subjects were instructed to inhale to total lung capacity before exhaling as forcefully, as quickly, and as fully as they could. They were also told to indicate (usually by blinking or by nodding their head) when they had reached the end of inhalation and were about to start exhalation to enable the researcher to start recording on the spirometer. In the case of the AFES-assisted tests, this was also the signal for the researcher to turn on the AFES. Subjects were encouraged throughout each manoeuvre. Three valid attempts were counted when the subject had performed three FVC manoeuvres in which the sum of the FVC and FEV_1 were within 20% of each other.

3.5.2 Continuous Breathing Tests

To conduct the continuous breathing tests the assessment control system was used (see Section 3.3, page 55).

Cough Test

Three sets of coughing were done: unassisted cough, CFT cough and CIT cough. For each set, subjects were instructed to cough, with maximum effort, five to six times. Subjects were told that they could take as many normal breaths as they would like between coughs. A minimum of thirty seconds of normal breathing separated each set of coughing. The researcher monitored the CPF of each cough throughout each set and gave feedback to the subject to encourage maximum effort for each cough.

In most cases, stimulation for the relevant coughs was applied automatically as described in Section 3.2. However, if it was not possible to set suitable triggers for automatic stimulation, then AFES was triggered manually by the researcher

to coincide with the glottal closure phase of the cough and to last approximately one second.

Quiet Breathing Test

Approximately seven minutes of continuous quiet breathing was recorded for this test. This consisted of one minute of unassisted quiet breathing which was followed by five minutes of AFES-assisted quiet breathing and concluded with a further one minute of unassisted quiet breathing. Subjects were instructed to breathe as naturally as possible during the test.

For the AFES-assisted quiet breathing, stimulation was triggered automatically as described in section 3.2.

3.5.3 Assessment Protocol for the First Three Subjects

Subjects S1, S2 and S3 completed a different assessment protocol from the other subjects (see Section 3.4.3). The assessment timeline for these subjects is shown in Figure 3.13.

MEP test
1) 3 Unassisted attempts
2) 3 AFES-assisted attempts

Cough test - 5 unassisted coughs
QB test – 1 minute unassisted
FVC test
1) 3 Unassisted attempts
2) 3 AFES-assisted attempts
Cough test - 5 unassisted coughs
QB test – 3 minutes unassisted
Cough test - 5 CIT coughs
QB test – 3 minutes unassisted
Cough test - 5 CIT coughs
QB test – 3 minutes unassisted
QB test – 3 minutes unassisted
QB test – 10 minutes AFES-assisted
MEP test
1) 3 Unassisted attempts
2) 3 AFES-assisted attempts

Figure 3.13: Time line of the assessment session for subjects S1, S2 and S3

The differences in assessment protocol, aside from the differences in assessment

timeline, between the protocol for S1, S2 and S3 and the rest of the subjects are described in Table 3.2

3.6 Training Protocols

The on-board programme on the stimulator was used to conduct the training sessions. Training sessions were normally completed while subjects were seated in their wheelchair although some sessions were completed while the patient was supine in their bed (see Section 3.4). The stimulation frequency was set at 30 Hz for all of the training sessions. Since the rate of muscle fatigue increases with stimulation frequency [67], the stimulation frequency was set at 30 Hz so as to produce a tetanic contraction of the abdominal muscles throughout the training sessions. The stimulation current settings that were used in the assessment session prior to each week of training were used. At the start of a training session, the electrodes were placed on the subjects abdomen (as shown in Figure 3.2) and the stimulation current settings were checked to ensure an even contraction across the abdomen. The on-board stimulation programme's parameters were adjusted so that stimulation would coincide with exhalation, and the stimulation was turned on. For S1, S2, and S3 the pulse width was increased until a strong visual contraction of the abdominal muscles was observed. For subsequent subjects the pulse width was quickly increased from 20 μs to the level which had produced the highest MEP during the previous assessment session. Throughout the training session the pulsewidth was increased further to maintain the same visual contraction of the abdomen.

   Training sessions were carried out up to five times per week. The duration of training was twenty minutes per day in the first week, forty minutes per day in the second week and sixty minutes per day in the third week. The design of the training program, in which the training volume was progressively increased every week, was chosen according to the principles of progressive overload [79]. Training was either carried out by a researcher for inpatients of the QENSIU, or left to the responsibility of the patients if they were living at home. In both cases a training diary was kept to record the stimulation current, stimulation pulse width, duration of training and comments from either the patient or researcher.

Table 3.2: The differences in protocols used for S1 - S3 and S4 - S16

Difference	S1–S3	S4–S16	Justification
Starting Pulse Width	Set at the level that produced a strong visible contraction	Set at the value that produced the greatest AFES-assisted MEP	To improve the consistency of the stimulation intensity between subjects and across the assessment sessions within a single subject.
FVC and MEP Tests	Three attempts only were collected	The tests were repeated until three valid attempts were collected	To improve the repeatability of the test.
Coughing Tests	Two sets of five unassisted cough and two sets of CIT cough were collected	One set of five of each unassisted cough, CFT cough and CIT cough were collected	To allow CIT, CFT and unassisted cough to be compared
Quiet Breathing Tests	Three periods of unassisted quiet breathing followed by one period of AFES-assisted quiet breathing were collected	One period of AFES-assisted breathing was collected in between two periods of unassisted quiet breathing.	To allow the transition from AFES-assisted breathing to unassisted breathing to be evaluated.

3.7 Analysis

In this section the general analysis methods of the recorded data is described. Full details of the specific analysis used for each respiratory test are given in the relevant chapters.

3.7.1 Breath Analysis

Examples of spiro_D and spiro_V (described in Section 3.2.2) recorded from the spirometer are shown in Figure 3.14 and Figure 3.15 respectively. From these variables, continuous breath-by-breath volume and flow rate were calculated using the following method.

1. As illustrated in Figure 3.14, the location of the zero crossings corresponding to the start and end of inhalation and exhalation were calculated from spiro_D.

2. Spiro_V was zero phase filtered using a forward and reverse pass of a 5th order simple moving average filter.

3. Using the zero crossings, spiro_V was reshaped into breath-by-breath volume profiles (illustrated in Figure 3.16).

4. Using the sampling time, the breath-by-breath volume was differentiated to obtain air flow rate (illustrated in Figure 3.17)

From the breath-by-breath volume and flow rate the following respiratory measures were derived. These are described below and illustrated in Figure 3.18 and Figure 3.19.

Inhaled Volume (V_I) The total volume of air inhaled in a breath, measured in litres (L).

Exhaled volume The total volume of air exhaled in a breath, measured in litres (L). This quantity is used interchangeably with V_T throughout this thesis.

Inspiratory time the duration of inhalation, measured in seconds (s).

Expiratory time the duration of exhalation, measured in seconds (s).

Breathing period the sum of inspiratory and expiratory time, measured in seconds (s).

Fractional Inspiratory Time ($T_{I/TOT}$) Inspiratory time divided by breathing period.

Breathing Rate (BR) The number of Breaths per Minute (BPM). Calculated for each breath by dividing sixty by breathing period.

Minute Ventilation ($\dot{V}$) The volume of air exhaled every minute, measured in Litres per minute (L/min). Calculated for each breath by multiplying exhaled volume by the BR.

Forced Exhaled Volume in One second (FEV_1) The volume of air exhaled in the first second of exhalation, measured in litres (L). FEV_1 was normally calculated from the point at which flow rate became positive. During coughing, however, flow rate often became positive during the glottal closure phase of the cough. To ensure that the calculation of FEV_1 during a cough did not include the glottal closure phase of the cough, the start of exhalation was taken as the first sample of positive flow in which the next four samples showed a progressive increase in flow rate (see Figure 3.19). If the duration of exhalation was less than one second, this measure was not calculated.

Peak Expiratory Flow (PEF) The maximum flow rate during exhalation taken from the filtered flow rate signal, measured in litres per second (L/s)

In addition to the above measurements the maximum stimulation pulse width and the maximum partial pressure of carbon dioxide exhaled (i.e. ET_{CO_2} during each breath was recorded.

Individual breaths were sorted into unassisted breaths and stimulated breaths. At the end of this stage of the analysis a dataset of unassisted and AFES-assisted breaths was available for each respiratory test completed during the assessment.
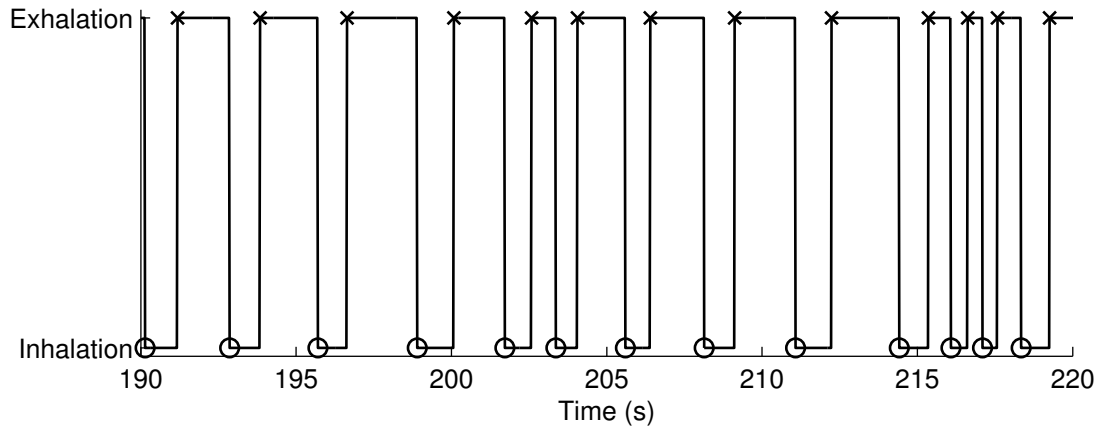
Figure 3.14: Example of the spiro_D output from the spirometer when used in live mode. The x's indicate the start of exhalation and the o's indicate the start of inhalation.
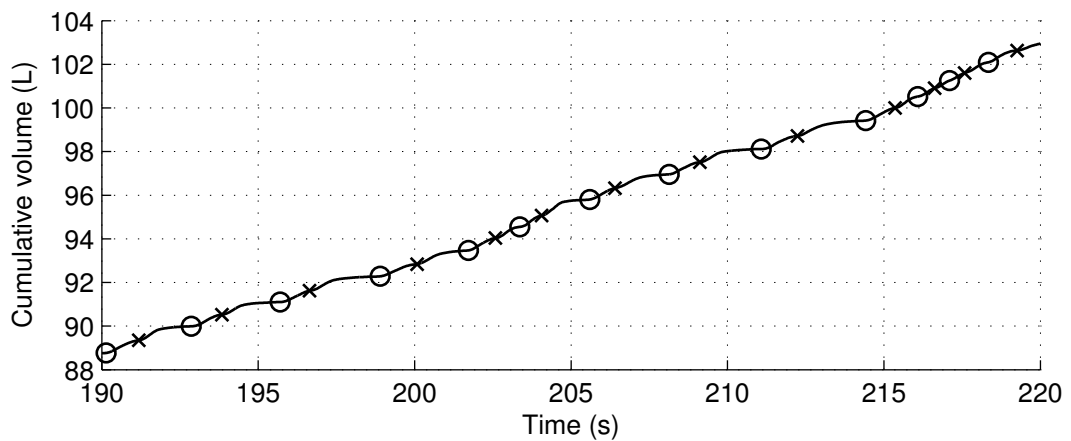
Figure 3.15: Example of the spiro_V output from the spirometer when used in live mode. The x's indicate the start of exhalation and the o's indicate the start of inhalation.
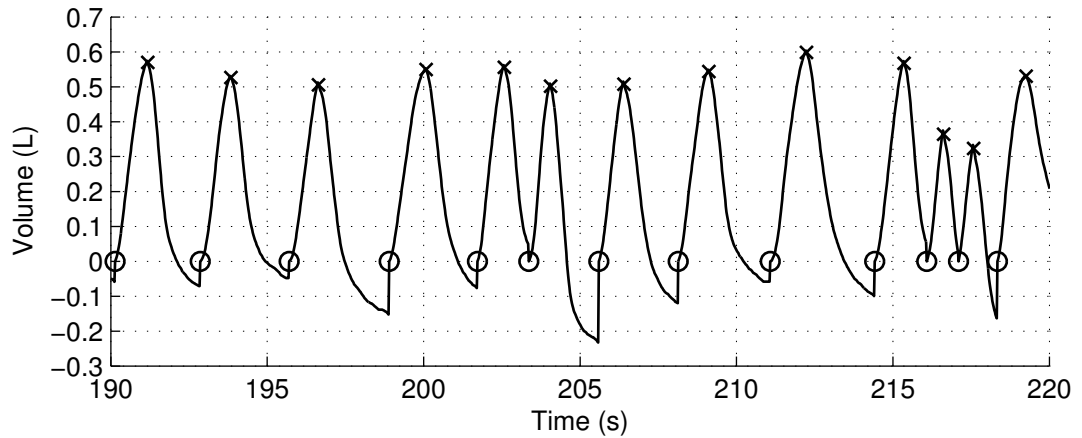
Figure 3.16: Example of the breath-by-breath volume calculated from spiro_V and spiro_t. A positive gradient indicates an inhalation and a negative gradient indicates an exhalation. The volume trace has been reset to zero at the start of every inhalation. The x's indicate the start of exhalation and the o's indicate the start of inhalation.
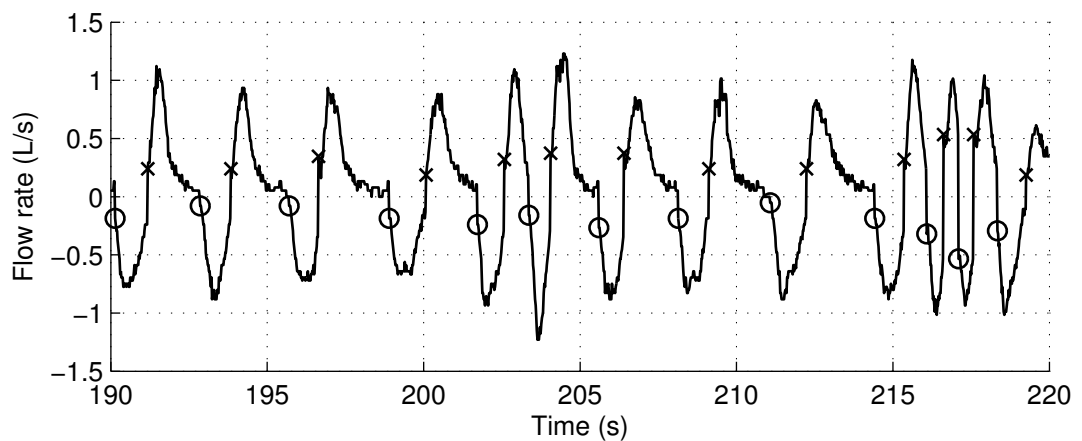
Figure 3.17: Example of the continuous flow rate calculated from spiro_V and spiro_t. Negative flow indicates inhalation while positive flow indicates exhalation. The x's indicate the start of exhalation and the o's indicate the start of inhalation.
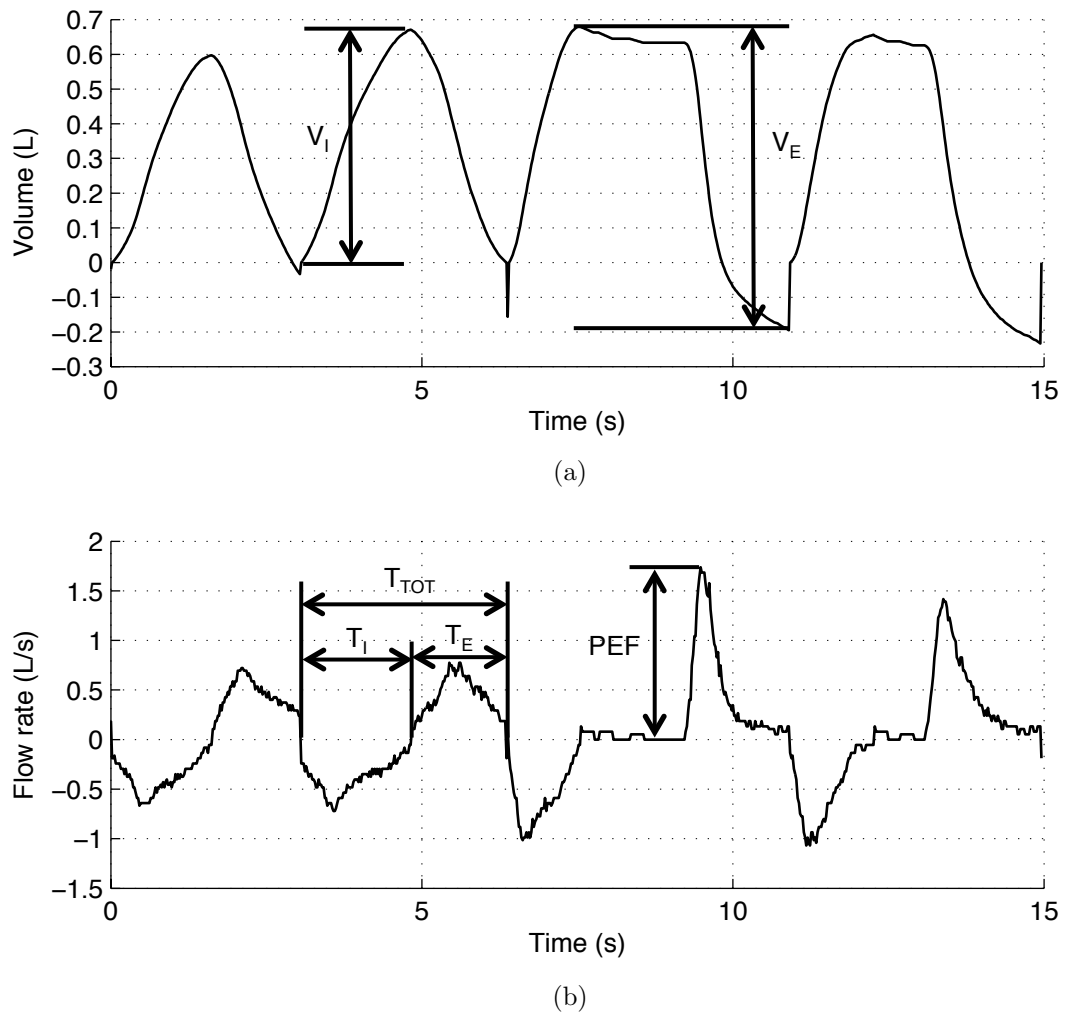
Figure 3.18: Respiratory measures calculated from the spirometer when used in 'live mode'. The plots show two normal quiet breath followed by two coughs. (a) shows the breath-by-breath volume; a positive gradient indicates inhalation and a negative gradient indicates exhalation. The volume has been reset to zero at the start of every inhalation. (b) shows the breath-by-breath flow rate. A negative flow rate corresponds to an inhalation while a positive flow rate corresponds to exhalation.
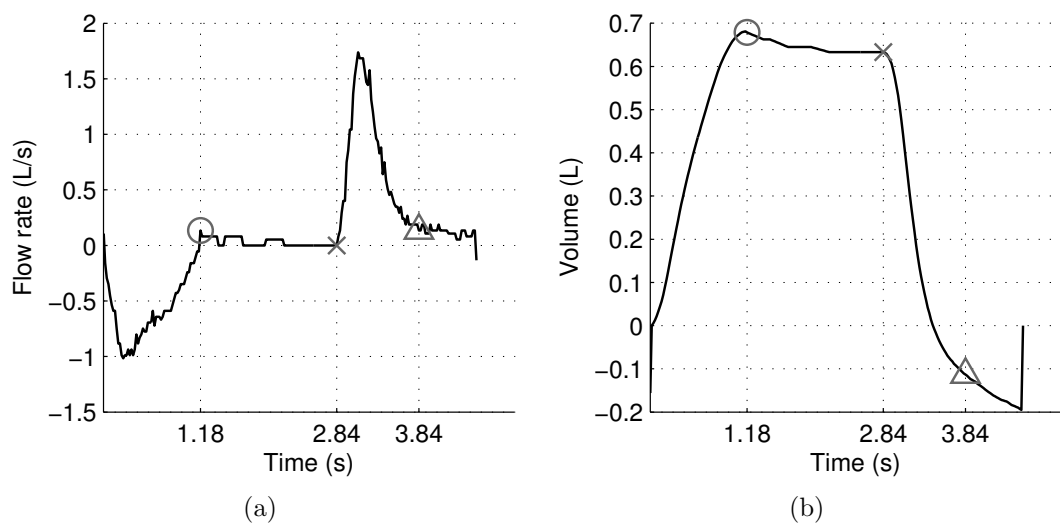
Figure 3.19: Example of how FEV_1 was calculated. In each of the subfigures, the circle marks the zero crossing which indicates the start of exhalation, the cross marks the start point used for the calculation of FEV_1 and the diamond marks the end point used for the calculation of FEV_1.

3.8 Study Performance

3.8.1 Subjects

This study included sixteen subjects whose details are given in Table 3.3. The recruitment of subjects started in March 2009 and continued for twenty-one months. The subjects recruited included current inpatients at the Queen Elizabeth National Spinal Injuries Unit (QENSIU), Southern General Hospital, Glasgow and outpatients who lived in the local area.

Table 3.3: Subject details. Age and time post injury are given at the time of the first study assessment session. *: subjects who were outpatients of the hospital; †: subjects who did not complete the entire protocol (see Section 3.8).

ID	Sex	Age [years]	Height [cm]	Level of injury	ASIA	Post-injury [months]	Smoker
S1	M	18	183	C4/5	A	5	N
S2	M	31	180	C5/6	C	2	N
S3	M	73	180	C4	A	5	N
S4†	M	56	186	C4	A	3	N
S5*	M	24	168	C4	A	94	N
S6†	M	52	173	C4	A	4	N
S7	M	54	187	C6	C	9	N
S8	M	53	178	C3	C	4	N
S9*	M	18	173	C6	A	27	N
S10	M	21	183	C6	A	5	Y
S11	M	18	183	C6	C	3	N
S12	M	68	168	C4	A	3	N
S13†	F	51	168	C5	C	3	N
S14	F	53	183	C6	C	3	N
S15*	M	32	178	C5	A	36	Y
S16†	M	16	178	C5	A	4	N
Mean	-	39	178	-	-	13	-
S.D	-	19	6	-	-	24	-
Median	-	42	179	-	-	4	-
Range	-	16 - 68	168 -187	-	-	2 - 94	-

Out of the seventeen subjects who were approached, sixteen were recruited into the study and twelve subjects completed the full study protocol. This is illustrated by the consort diagram in Figure 3.20.

One subject was approached but was determined not eligible as no visual contraction of her abdominal muscles was observed in response to AFES. S11 completed the study but missed out assessment A3. However, he moved from the twenty minute training sessions to the forty minute training sessions according to
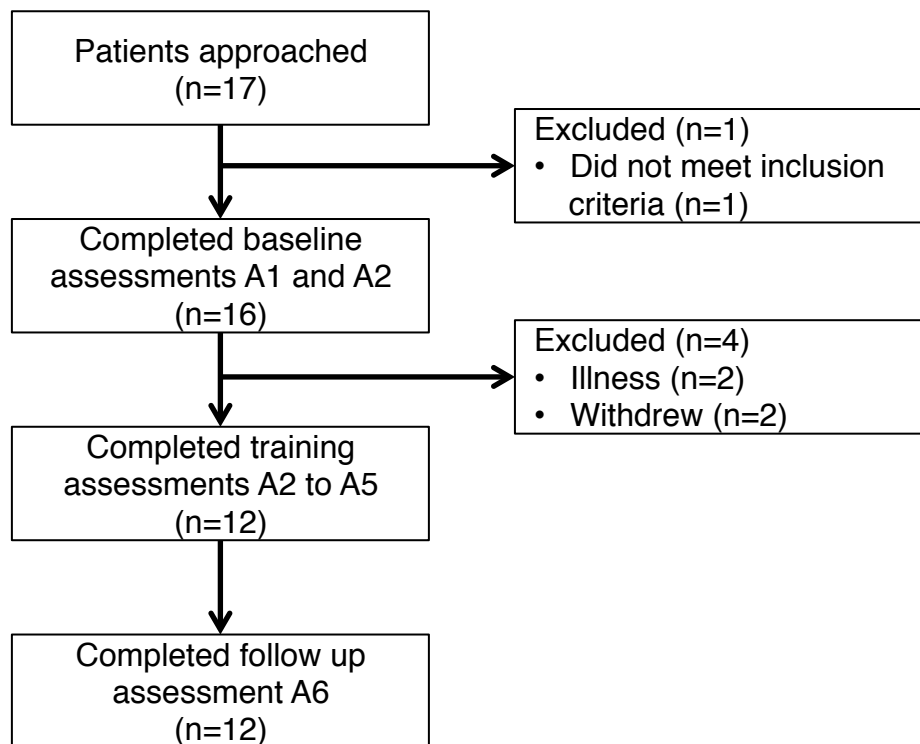
Figure 3.20: Consort diagram for the study.

the study protocol. Subjects S4, S13 and S16, left the study after A3 and S6 left the study after A4. S4 and S6 both left the study as a result of illness urelated to the study. S13 withdrew from the study for personal reasons. S16 reported increased spasms coincidental with the start of the study, although the subject's medical team were unclear whether it was caused by AFES as this subject already had a history of significant muscle spasticity.

3.8.2 Subject Compliance

The mean number of days that elapsed between the assessment sessions is given in Table 3.4. To calculate the mean days between A2 and A3 and between A3 and A4 for S11, a virtual A3 assessment was created at the time point at which the subject would have completed A3 had he been able to do so. Table 3.4 demonstrates that the average number of days spent between assessments was greater than prescribed. Since all assessments had to be completed while the subject was sitting in their wheelchair bed rest was the major cause of the delay. Other factors which led to delays between the assessment sessions were illness and general fatigue.

The largest deviations from the prescribed periods are as follows:

- The control period was longer than prescribed for S19, S10 and S16. For S9 this was 13 days while for S10 and S16 this was 21 days.

- The period between A2 and A3 was longer than prescribed for S4 and S11. For S4 this period lasted 22 days and for S11 this period lasted 11 days. The period between A2 and A3 was only 5 days for S15.

- The period between A3 and A4 was longer than prescribed for S8 and S15. For S8 this period lasted 9 days and for S15 this period lasted for 10 days.

- The period between A4 and A5 was longer than prescribed for S3, S5, S8, and S10. For S3 and S5 this period lasted for 14 days and for S8 and S10 this period lasted for 10 days.

- The follow up phase was lasted for 29 days for S2.

Table 3.4: Average number of days between assessment sessions for different subsets of the total subject pool. $A_{a,b}$ denotes the period between assessment a and assessment b. N signifies the number of subjects in each subset. The prescribed number of days between each assessment session is given at the top of the table for comparison. SD: standard deviation

Group	N	Mean days in period (SD)				
		$A_{1,2}$	$A_{2,3}$	$A_{3,4}$	$A_{4,5}$	$A_{5,6}$
Prescribed	-	7	7	7	7	21
All recruited subjects	16	9.1	8.1	7.5	8.7	21.8
		(4.8)	(3.8)	(1.0)	(2.8)	(2.37)
Subjects that completed the study protocol	12	8.7	7.3	7.5	8.7	21.8
		(4.3)	(1.4)	(1.0)	(2.8)	(2.4)

Table 3.5: Average number of minutes of received abdominal FES during each week of training. The mean and standard deviation for different subsets of the total subject pool are presented for each of the three weeks of training and for the total training period. N stands for the number of subjects in each subset. SD: standard deviation

	N	Mean FES minutes (SD)			
		Week 1	Week 2	Week 3	Total
Four days of training for the prescribed duration	-	80	160	240	480
All recruited subjects	16	88 (43)	155 (35)	241 (77)	395 (177)
Subjects that completed the study protocol	12	79 (10)	158 (34)	241 (77)	478 (130)

The mean minutes of AFES received during each week of training are given in Table 3.5. The results in this table are also presented on the assumption of

a virtual A3 for S11. Three subjects, S7, S10 and S14, completed their training during their normal hand therapy sessions. As the mean training times in the table suggest, most subjects had four training sessions in each week of training. The following subjects deviated from this:

Week 1 S1, S6 and S10 had three training sessions totaling 60 minutes, S11 had five training sessions totaling 100 minutes, and S4 has 13 training sessions totaling 245 minutes.

Week 2 S3 had three training sessions totaling 90 minutes, S1 and S6 had three training sessions totaling 120 minutes, S8 had five training sessions totaling 200 minutes and S5 had six training sessions totaling 227 minutes.

Week 3 S1 had three training sessions totaling 180 minutes, S7 and S8 had three training sessions totaling 190 minutes, S12 had four training sessions totaling 200 minutes, and S5 had eight training sessions totaling 475 minutes.

In general, subjects managed to perform the respiratory tests in the assessment session well. However, S8 experienced claustrophobia while wearing the face mask and refused to have it fastened using the hair net. Therefore, the mask had to be held tightly in place by a researcher during the FVC test and the continuous breathing tests. Other deviations from the assessment protocol, related to the specific breathing tests, are presented in the relevant chapter.

3.8.3 AFES Issues

In almost all cases, subjects tolerated the stimulation well and a good contraction of the abdominal muscles was achieved. However, there were AFES issues for the following subjects.

S7 This subject required the maximum stimulation current to be applied for every stimulation channel. Although using the maximum current evoked a strong response from the abdominal muscles on the left side of the patient, the contraction of the muscles on the right side was noticeably weaker. This may have been caused by poor contact between the electrodes and the skin as this patient had a large amount of body hair on the abdomen. Alternatively, it may also have been because the abdominal muscles on the right side of the abdomen were weaker than the muscles on the left side.

S8 This subject had intact sensation on the right side of his abdomen, which limited the stimulation current that could be applied to it. Therefore, it

was not possible to obtain an even contraction across the abdominal muscles in this subject. In the third week of training, stimulation to the right side of the rectus abdominis was removed, this allowed the intensity to the right external oblique muscle to be increased and a more even contraction was achieved.

S16 This subject reported increased spasms after the completion of an AFES training session. Since this subject had a significant history of muscle spasticity, the subject's medical team were unclear as to whether this effect was a consequence of AFES or coincidental with the start of the study.

3.8.4 Non Respiratory Effects

Three subjects, S7, S14 and S15, reported a self-perceived increase in abdominal muscle tone following the training. These subjects regarded this increased abdominal tone as useful in helping with tasks that required stability of the upper body, for example wheelchair transfers. Furthermore, they enquired whether there was a stimulator they could purchase for use at home.

3.9 Discussion

In this chapter, the methods that were used to investigate the acute and chronic effect of AFES in spontaneously breathing tetraplegics have been described. In addition the results which describe the adherence to the overall protocol of the study have been presented. The results from the respiratory tests conducted will be presented in separate chapters. Specifically the FVC and MEP test results will be presented in Chapter 4, the results from the cough test will be presented in Chapter 5 and the results from the quiet breathing test will be presented in Chapter 6.

The greatest challenge in conducting this study was in working with the patients who were recently injured and currently participating in standard rehabilitation. This created two issues.

1. Finding a suitable time to conduct the assessment and training sessions was often difficult.

2. Dealing with secondary complications associated with the injury, in particular bed rest, resulted in deviations from the protocol.

Despite these problems, the majority of the subjects recruited were both able to complete the study and to follow the training programme with reasonable accuracy. This demonstrates the benefits of passive training which stimulates only the abdominal muscles. The practical advantages are:

1. Patients were able to complete their training sessions during their normal hand therapy sessions. This would not have been possible if an active training programme had been used, such as the approach used by Zupan et al. [159].

2. If the pectoral muscles had been stimulated, as proposed by Cheng et al. [27], this would have required a longer set up time and patients may also have required that the electrodes be applied in private.

On these practical aspects alone the author believes that the training paradigm proposed in this thesis is superior to previous training paradigms.

The non-respiratory effects of the AFES training programme reported by some patients are encouraging. Although conclusions cannot be drawn, this evidence highlights an interesting question: are the patients likely to continue with the intervention unsupervised?

Chapter 4

Study 1: Clinical Respiratory Test Results

4.1 Introduction

The FVC and MEP tests are standardised clinical tests that are used to measure respiratory function (see Section 2.2.2, page 19). The FVC test is used as a diagnostic tool to assess the impact of disease on respiratory function and to assess the effect of therapeutic interventions on the respiratory system [112]. The MEP test is used to measure expiratory muscle strength [53]. The outcome measures from these tests have been shown to be substantially reduced in tetraplegic SCI compared with normal values for an able-bodied population [94]. Furthermore, an improvement in these indicators has been shown to be positively correlated with a reduction in respiratory complications in tetraplegia [27].

It has previously been shown that an FES respiratory muscle training programme can improve tetraplegic patients' unassisted FVC and MEP test outcomes [27, 159]. Two types of training programme have beed used previously:

1. Zupan et al. [159] combined breathing exercises with AFES, an active training programme.

2. Cheng et al. [27] applied a repeating pattern of FES to the pectoral and abdominal muscles, a passive training programme.

The effect of an exclusive AFES passive training programme on unassisted FVC and MEP outcome measures has not been studied but has two main advantages over the other programmes: (i) it is a passive, which allows the patient to participate in other activities at the same time as training; (ii) it is quicker and easier to

apply as it only requires stimulation to one muscle group rather than to several muscle groups. This is an important consideration in a busy hospital.

Previous work has shown that AFES-assisted FVC and MEP test outcomes are greater than unassisted test outcomes in patients with tetraplegia [85, 87, 159]. This effect has been shown only in single session studies and the effect of repeated chronic use of AFES on AFES-assisted outcome measures has not been investigated. If the difference between the AFES-assisted and unassisted outcome measures became greater through chronic use of AFES, then it would be clear that AFES was becoming increasingly effective and that an AFES neuroprosthesis, for example the system proposed by Gollee et al. [57], would also become more effective over time.

Leading on from previous work, this chapter presents the results of a three week passive AFES training programme on FVC and MEP test outcomes. The primary aims of this study were to determine the effect of the training programme on:

1. The unassisted FVC and MEP test outcome measures.

2. The AFES-assisted FVC and MEP test outcome measures.

3. The AFES-assisted FVC and MEP test outcome measures relative to their corresponding unassisted outcome measures.

The secondary objective of this study was to verify that AFES-assisted FVC and MEP outcome measures were greater than their respective unassisted outcome measures.

4.2 Methods

The FVC and MEP tests and the study protocol are described in Chapter 3.

The dependent outcome measures were FVC, FEV_1, PEF and MEP. All results were expressed as absolute values and as a percentage of the predicted value for a healthy subject (%pred.) [17, 69]. For each outcome measure the mean of the three valid recordings made on each assessment session was calculated. Results representing the difference between unassisted and AFES-assisted outcome measures are denoted with a ΔAFES prefix.

4.2.1 Main Analysis

The main focus of the study was to investigate the change in unassisted, AFES-assisted, and ΔAFES FVC and MEP test outcome measures over course of the training period, and to compare this change to any change that occurred during the control and follow up periods of the study. This analysis included only subjects that completed the final assessment session (A6) and that missed no more than one assessment session during the study.

4.2.2 Secondary Analysis

The secondary objective of this study was to verify previous authors' finding that AFES-assisted FVC and MEP test outcome measures were greater than their respective unassisted outcome measures (i.e. ΔAFES was positive) [85, 87, 159]. This analysis included all of the subjects who completed at least one of the A1 and A2 assessment sessions. For each eligible subject the mean was taken over A1 and A2.

4.2.3 Statistics

The data from each assessment session was tested for normality using the Shapiro-Wilks test. Based on the finding that data on some assessment sessions was not normally distributed, non-parametric statistical tests were used for hypothesis testing. Data sets with more than one missing value were discarded. Missing data points were replaced by the value from the previous assessment (last value carried forward). The Wilcoxon Signed Rank test was used for paired comparison testing at baseline. The repeated measures Friedman test was used to test for longitudinal changes in the outcome measures through the study. In the case of significance, post hoc multiple comparisons were performed using the Tukey-Kramer honestly significant difference procedure. To test the validity of using the last value carried forward to replace missing data a sensitivity analysis was done by also completing the statistical analysis after removing subjects that missed at least one assessment from the data set. For all tests $p < 0.05$ was regarded as statistically significant.

4.3 Results

4.3.1 Missing Data

The MEP test results for S1, S2 and S3 were not collected due to technical problems and the MEP results from S8 were discarded as unreliable because this subject had difficulties performing this test. The FVC test results were discarded for S10 as he started swinging his upper body forward while performing the test in later assessment sessions. As described in Section 3.8, S11 did not complete A3.

Unassisted FVC, FEV_1 and PEF were discarded on A3 for S1, and on A2 for S2 and S3 because only one usable attempt was collected. In addition, AFES-assisted FVC, FEV_1 and PEF were discarded on A1, A2 and A3 for S1, on A1 for S2 and S8, and on A2 for S3 because only one usable attempt was collected.

4.3.2 Subject Pools

Table 4.1 shows which subjects were used in each part of the analysis after removing datasets that contained more than one missing data point and excluding subjects who did not finish the study from the longitudinal data analysis.

Table 4.1: Subjects used in each stage of the analysis after accounting for missing data

Analysis	N	Subjects
Unassisted analysis	11	S1-S3, S5, S7-S9, S11, S12, S14, S15
AFES analysis	10	S2, S3, S5, S7-S9, S11, S12, S14, S15
ΔAFES longitudinal analysis	9	S3, S5, S7-S9, S11, S12, S14, S15
ΔAFES baseline analysis	15	S2-S16

4.3.3 Unassisted Results

Table 4.2 details the group mean unassisted results on each assessment session. As can be seen from the table there was very little change over the control phase (between A1 and A2) for all of the outcome measures. Over the training phase (between A2 and A5) FVC, FEV_1 and PEF increased, while there was little change in MEP. During the follow up phase (between A5 and A6), there was very little change in FVC, FEV_1 and PEF, while MEP increased slightly. Table 4.2 also shows the p-value from the Friedman statistical analysis. The longitudinal changes in FVC, PEF, and MEP were significant. Post-hoc multiple comparison

testing for FVC found a significant difference from A2 to A5 and A6. For PEF, a significant difference was found between A2 and A6. Post-hoc testing did not find any significant differences for MEP.

Table 4.2: The group mean ($\pm$ standard deviation) unassisted FVC, FEV_1, PEF, and MEP test results on each assessment session. p is the probability that there was no change in each of the outcome measures throughout the study calculated using the Friedman test.

	A1	A2	A3	A4	A5	A6	p
FVC (L)	1.79 ± 1.04	1.81 ± 1.27	1.85 ± 0.96	1.98 ± 1.23	2.17 ± 1.27	2.23 ± 1.39	<0.01
FVC (%pred.)	35.12 ± 18.96	35.33 ± 22.83	36.50 ± 18.37	38.87 ± 22.44	42.70 ± 23.29	43.88 ± 25.80	
FEV_1 (L)	1.16 ± 0.55	1.17 ± 0.54	1.22 ± 0.59	1.22 ± 0.63	1.35 ± 0.59	1.36 ± 0.59	0.06
FEV_1 (%pred.)	28.00 ± 12.84	28.18 ± 12.74	29.62 ± 15.95	29.51 ± 15.10	32.43 ± 14.57	33.11 ± 14.82	
PEF (L/s)	2.09 ± 1.19	2.07 ± 1.30	2.29 ± 1.53	2.23 ± 1.40	2.46 ± 1.56	2.43 ± 1.50	0.04
PEF (%pred.)	22.57 ± 13.59	22.31 ± 14.91	25.03 ± 18.47	24.25 ± 16.84	26.52 ± 18.24	26.45 ± 17.92	
MEP (cmH_2O)	25.42 ± 16.57	24.83 ± 17.06	22.25 ± 13.32	24.29 ± 15.39	24.75 ± 14.25	28.17 ± 18.09	0.03
MEP (%pred.)	19.59 ± 15.65	19.17 ± 15.91	17.31 ± 14.07	19.05 ± 16.30	19.25 ± 15.27	21.40 ± 15.96	

Figure 4.1 illustrates the unassisted individual subject results over the course of the study. As can be seen from the figure there was considerable inter and intra subject variation for each of the outcome measures.

Effect of AFES Training on Different Sub-Populations

Figure 4.2 shows the mean changes from A1 in the unassisted outcome measures for different patient sub-populations, which include motor complete tetraplegics, motor incomplete tetraplegics, tetraplegics with an injury level at or above C4 (i.e a high level injury) and tetraplegics with an injury at or below C5 (i.e. a low level injury). The demographics of the patient sub-groups are shown in Table 4.3.

Table 4.3: Demographics of the sub-populations of subjects. Where applicable results are expressed as mean $\pm$ standard deviation.

	Complete	Incomplete	High	Low
N	7	5	4	8
Sex (male/female)	7/0	6/1	4/0	7/1
Age (years)	36 ± 24	42 ± 16	55 ± 22	30 ± 15
Height (cm)	176 ± 7	182 ± 3	174 ± 6	181 ± 4
Injury level (high/low)	3/4	1/4	4/0	0/8
ASIA (A/C)	7/0	0/5	3/1	4/4
Time Post Injury (months)	25 ± 33	4 ± 3	27 ± 45	11 ± 13
Smoker/Non-smoker	2/5	0/5	0/4	2/6

There was an increase in all of the outcome measures between A5 and A6 for the tetraplegic patients with a motor complete SCI. In contrast there was a decrease in all of the outcome measures for the tetraplegic patients with a motor incomplete SCI. Similarly FEV_1 and PEF increased between A5 and A6 for the
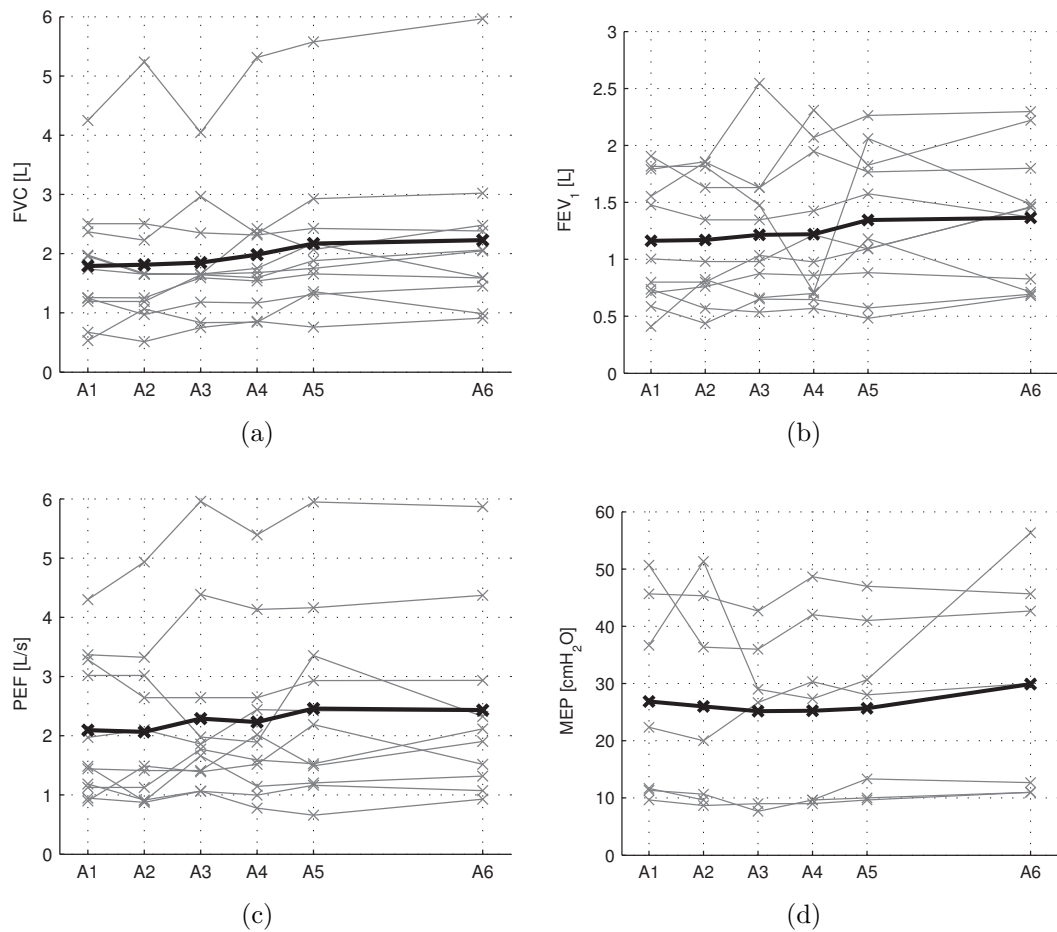
Figure 4.1: Unassisted FVC, FEV$_1$, PEF and MEP results. The grey lines represent individual subjects and the black line represents the group mean.

tetraplegic patients with a high level SCI and decreased for the patients who have a low level SCI. No other clear differences between the subject groups were observed.
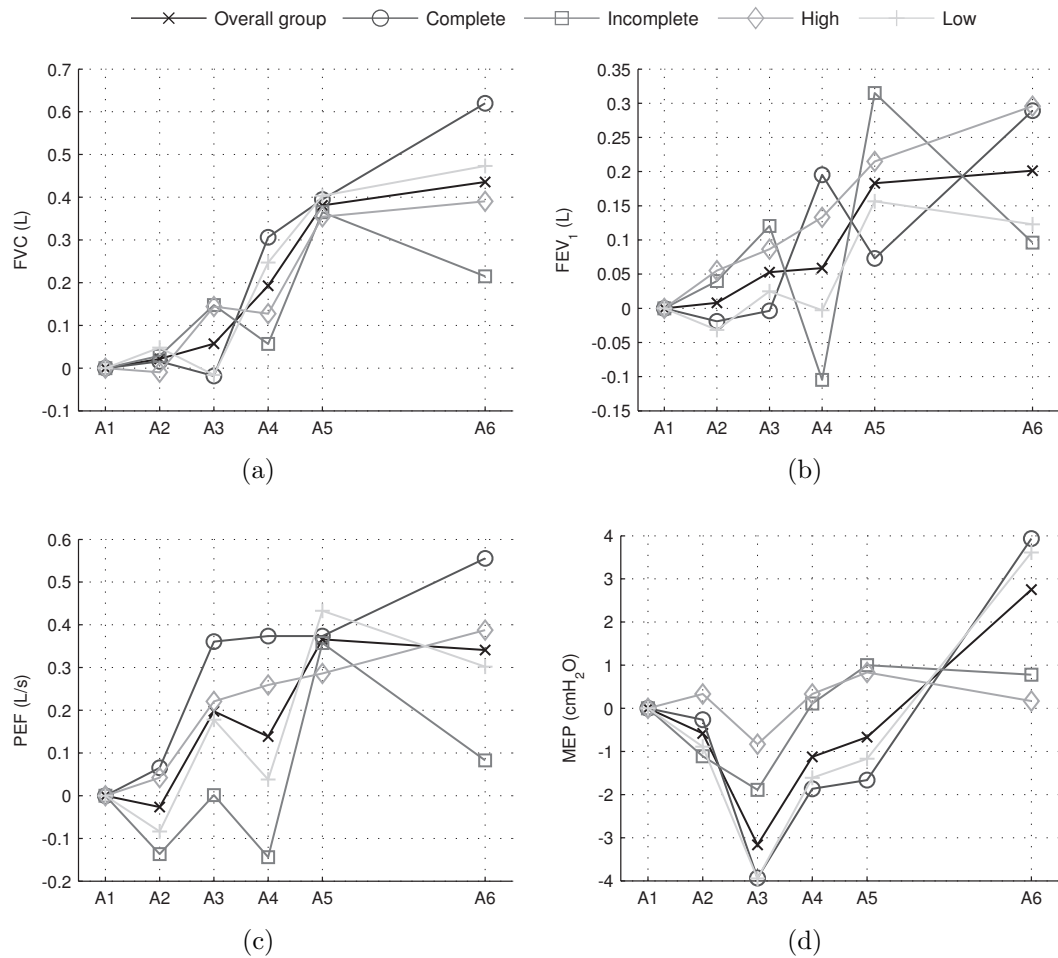
Figure 4.2: Change in unassisted FVC, FEV_1, PEF and MEP test results stratified by different patient groupings

4.3.4 AFES-Assisted Results

Table 4.4 gives the group mean AFES-assisted results over the course of the study. The change in AFES-assisted outcome measures followed a similar trend to that of the unassisted results. Only the longitudinal change in FVC was found to be significant, for which multiple comparison testing found A2 to be significantly different from both A4 and A5.

The inter and intra subject variations of the AFES results were of a similar magnitude to the unassisted results (illustrated in Figure 4.1). In addition no obvious difference was observed in the AFES-assisted response to training for different subject sub-populations.

Table 4.4: Group mean ($\pm$ standard deviation) AFES-assisted FVC, FEV$_1$, PEF and MEP results on each assessment session

	A1	A2	A3	A4	A5	A6	p
FVC (L)	1.93 ± 1.12	1.98 ± 1.32	2.05 ± 1.12	2.34 ± 1.44	2.36 ± 1.43	2.31 ± 1.44	<0.01
FVC (%pred.)	38.39 ± 20.78	39.74 ± 24.85	41.31 ± 21.61	46.91 ± 26.94	47.39 ± 27.03	46.62 ± 27.50	
FEV$_1$ (L)	1.26 ± 0.52	1.26 ± 0.54	1.31 ± 0.60	1.24 ± 0.54	1.48 ± 0.65	1.44 ± 0.65	0.57
FEV$_1$ (%pred.)	31.09 ± 12.25	31.04 ± 12.60	32.68 ± 15.78	31.08 ± 13.84	36.52 ± 15.38	36.13 ± 16.54	
PEF (L/s)	2.33 ± 1.14	2.37 ± 1.27	2.35 ± 1.55	2.45 ± 1.75	2.83 ± 1.70	2.83 ± 1.77	0.58
PEF (%pred.)	25.17 ± 13.12	25.67 ± 14.70	25.85 ± 18.65	26.83 ± 20.62	30.42 ± 19.06	30.87 ± 20.65	
MEP (cmH$_2$O)	28.67 ± 18.15	31.88 ± 16.45	27.88 ± 17.65	28.42 ± 16.27	33.38 ± 14.41	33.92 ± 18.75	0.29
MEP (%pred.)	21.42 ± 14.01	24.29 ± 15.80	22.06 ± 19.02	22.18 ± 16.78	25.75 ± 15.30	26.26 ± 18.49	

4.3.5 ΔAFES Results

Table 4.5 shows the group mean results at baseline. As shown in the table, AFES-assisted FVC, FEV$_1$, PEF, and MEP were significantly greater than their corresponding unassisted outcome measures.

Table 4.5: Effect of AFES on the FVC, FEV$_1$, PEF and MEP results at baseline. The results reported are the group mean $\pm$ one standard deviation of the individual subject results averaged over A1 and A2. p is the p-value from the comparison of the unassisted and AFES-assisted results using the Wilcoxon Sign Rank test

	Unassisted	AFES-assisted	ΔAFES	p
FVC (L)	1.76 ± 0.96	1.95 ± 1.00	0.19 ± 0.31	0.01
FVC (%pred.)	34.83 ± 17.43	39.53 ± 19.39	4.32 ± 7.51	0.01
FEV$_1$ (L)	1.17 ± 0.47	1.30 ± 0.45	0.10 ± 0.16	< 0.01
FEV$_1$ (%pred.)	28.38 ± 10.75	32.15 ± 10.38	2.74 ± 4.32	< 0.01
PEF (L/s)	2.04 ± 1.06	2.33 ± 1.05	0.23 ± 0.20	< 0.01
PEF (%pred.)	22.06 ± 11.86	25.22 ± 11.68	2.54 ± 2.12	< 0.01
MEP (cmH$_2$O)	20.31 ± 14.15	26.95 ± 14.90	6.64 ± 5.57	< 0.01
MEP (%pred.)	15.88 ± 12.94	20.79 ± 12.54	4.92 ± 4.43	< 0.01

Figure 4.3 shows the group mean unassisted and AFES-assisted outcome measures, and Table 4.6 gives the group mean ΔAFES outcome measures, at each assessment during the study. Though there were large differences between several assessment sessions (e.g. ΔMEP increased from 3.25 to 7.04 cmH$_2$O between A1 and A2), there were no clear trends in the change in ΔAFES throughout the study for any of the outcome measures. Accordingly, the changes in the outcome measures were not statistically significant.

Table 4.6: Group mean ($\pm$ standard deviation) ΔAFES FVC, FEV$_1$, PEF and MEP results on each assessment session

	A1	A2	A3	A4	A5	A6	p
ΔFVC (L)	0.10 ± 0.28	0.15 ± 0.45	0.19 ± 0.34	0.34 ± 0.51	0.13 ± 0.49	0.07 ± 0.44	0.39
ΔFEV$_1$ (L)	0.02 ± 0.13	0.07 ± 0.20	0.09 ± 0.15	0.02 ± 0.20	0.08 ± 0.30	0.08 ± 0.34	0.86
ΔPEF (L/s)	0.11 ± 0.26	0.20 ± 0.21	-0.01 ± 0.23	0.22 ± 0.49	0.19 ± 0.45	0.37 ± 0.54	0.23
ΔMEP (cmH$_2$O)	3.25 ± 7.16	7.04 ± 6.83	5.62 ± 6.32	4.12 ± 5.33	8.62 ± 9.62	5.75 ± 7.77	0.53
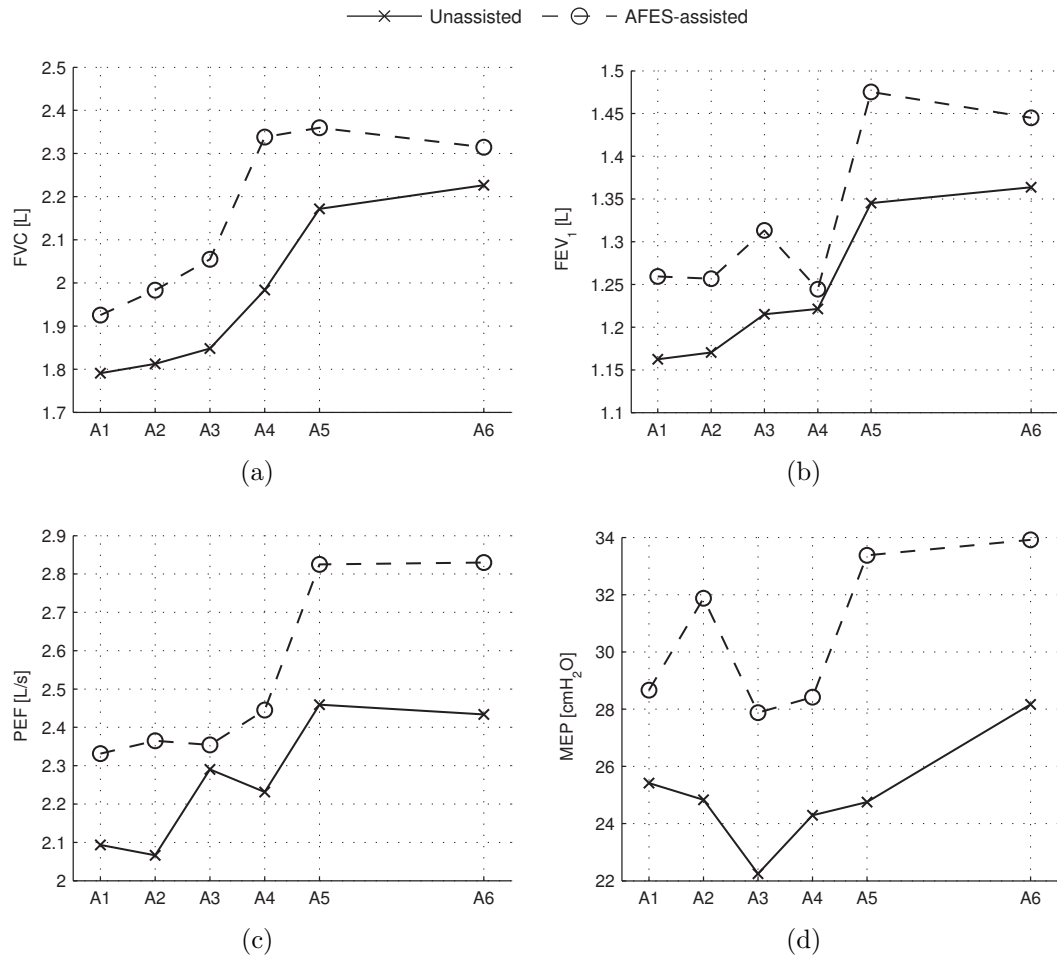
Figure 4.3: Group mean unassisted and AFES-assisted FVC, FEV_1, PEF and MEP results

4.3.6   Sensitivity Analysis

Table shows the p-values from the Friedman test performed on the data set in which subjects who had missed at least one assessment session were removed. This analysis confirmed that the change in unassisted and AFES-assisted FVC was significant. Contrary to the last value carried forward analysis, however, it found that the change in unassisted PEF was not significant and that the change in ΔAFES PEF was significant. All other results were in agreement between the two analysis methods.

Table 4.7: Results of the sensitivity analysis. The table shows the p-values from the Friedman test performed on the data set in which subjects who had missed at least one assessment session were removed.

	Unassisted	AFES	ΔAFES
FVC	0.0021	0.0098	0.3451
FEV_1	0.2262	0.2971	0.8989
PEF	0.0825	0.3347	0.0419
MEP	0.0872	0.1834	0.2771

4.4 Discussion

The aim of this study was to determine the effect of a passive AFES respiratory muscle training programme on unassisted and AFES-assisted standard clinical pulmonary function measures. Based on previous work it was hypothesised that the training intervention would improve unassisted FVC and MEP test outcome measures [27, 159]. In addition it was hypothesised that the training intervention would increase the absolute value of the AFES-assisted outcome measures, and the relative value of the AFES-assisted outcome measures compared with the unassisted outcome measures. This study found that both unassisted and AFES-assisted FVC were significantly augmented over the training period but a relative change between AFES-assisted and unassisted FVC was not found.

4.4.1 Unassisted Clinical Respiratory Tests

The results show a significant improvement in FVC of 20% over the training period (A2 to A5). An increase in unassisted PEF of 19% was also shown, however, since the sensitivity analysis did not agree with the original analysis, further research is needed to confirm the validity of this result. While there was also a tendency for FEV_1 to increase over the training period this was not statistically significant. In the one week pre-training control phase (A1 to A2) and the three week follow up phase (A5 to A6), no statistically significant changes in any of the outcome measures were found. This suggests that the change in FVC over the training phase was a response to the intervention rather than due to natural recovery, which can occur in the acute phase of SCI [86].

This study included a heterogeneous sample of patients with a mix of injury levels, time post injury and AIS grade which led to a large inter-subject variability. Despite this complex case mix the results show that FVC improved for all but one subject over the training phase. Furthermore the absolute changes during the training phase relative to baseline over the study were comparable for those

subjects with motor complete and those with motor incomplete tetraplegia. This suggests that AFES training is applicable for a wide demographic of tetraplegic patients.

There was an increase between A5 and A6 in all of the outcome measures for the motor complete tetraplegic subjects. This observation is surprising as motor complete patients are much less likely to regain function than motor incomplete patients. There is no clear explanation for this difference and it should be verified in a future investigation.

The subjects included in this study were unable to contract their abdominal muscles voluntarily. Therefore, it is unlikely that the increase in FVC was a result of increased abdominal muscle strength. Instead the author hypothesises that an increase in inhalation volume resulted in the increase in FVC. There are at least two possible explanations for an increase in inhalation volume:

1. The respiratory muscle training programme used in this study may have increased abdominal muscle mass, which has been shown to be reduced in tetraplegia [51]. Previous studies have shown an increase in the cross sectional area of the leg muscles in SCI individuals after eight weeks [46] or six months [131] of FES. Although these studies lasted longer than the present study it is feasible that the training programme used in this study increased the cross sectional area of the abdominal muscles. This would lead to greater support of the abdominal contents, which act as a fulcrum as the diaphragm contracts [154], placing the diaphragm in a better mechanical position to expand the lower lung. Inhalation capacity would be increased and in turn so would FVC.

2. The compliance of the lung was increased. During the training sessions abdominal stimulation was applied in synchrony with exhalation and this probably augmented V_T [57,58,134]. In turn the augmented V_T may have increased the compliance of the lung, making it easier for patients to expand their lungs. This mechanism is reported to be responsible for the reduction in weaning duration observed in patients who are ventilated with greater tidal volumes [120].

In this study, neither the mass of the abdominal muscles, nor the compliance of the lung were measured since the primary objective of this exploratory study was to investigate whether the training programme affected respiratory parameters. Future studies should aim to validate the positive findings of this study and

should also validate the explanatory mechanisms presented here by including measurements of abdominal muscle mass and lung compliance.

The average increase in unassisted FVC (20% increase) found in this study was similar to the results of one previous study [159] but smaller than in other previous studies [27, 87]. In addition, a previous similar study [27] found a statistically significant increase in unassisted FEV_1 and PEF, whereas the increase in unassisted FEV_1 and PEF was smaller in this study and not statistically significant. There are at least two possible explanations for these differences:

1. The three week training period in this study was shorter than the four week training period used in the comparison studies [27, 87, 159]. In the current study the increase in FVC, FEV_1 and PEF did not plateau which suggests that further benefits from the intervention might be achieved if training was continued over a longer period of time. In the case of FEV_1 and PEF this may lead to a statistically significant change.

2. The training modality used. The interventions used in previous work trained other respiratory muscles, for example the pectoral muscles, in addition to the abdominal muscles. This was accomplished either by using additional channels of electrical stimulation [27], or by using breathing exercises which inherently recruit other expiratory muscles in addition to the abdominal muscles [87, 159]. Expiration is known to be an active process in patients with a tetraplegic SCI below the level of C5 [50]. Therefore, in this group of patients the training modalities used in previous work probably offered an additional physiological benefit compared with the training programme used in the current study.

Decreases in FVC have also been observed in a previous similar study by Hascakova-Bartova et al. [70]. Although Hascakova-Bartova et al. agree that training increased abdominal bulk they concluded this would have a negative impact on the diaphragm. A major difference between the present study and the study by Hascakova-Bartova et al. was the initial FVC of the subjects studied, which was considerably greater in the study by Hascakova-Bartova et al. than in the present study.

4.4.2 AFES-Assisted Clinical Respiratory Tests

The second and third aims of this study were to determine whether a passive AFES respiratory muscle training programme increased (i) the absolute values

of the AFES-assisted outcome measures, and (ii) the relative value of the AFES-assisted outcome measures compared with the corresponding unassisted outcome measures. These aims were investigated by initially verifying that there was a difference between unassisted and AFES-assisted outcome measures before the intervention began. Subsequently, this study determined whether AFES-assisted outcome measures changed over the study period. Finally, the change in the differences between the unassisted and AFES-assisted outcome measures over the course of the study were investigated.

Acute Effect of AFES on Clinical Respiratory Tests at Baseline

The results of this study showed that the AFES-assisted FVC, FEV_1, PEF and MEP were significantly greater than their corresponding unassisted outcome measures. A significant difference between unassisted and AFES-assisted FVC, FEV_1 and PEF has been reported previously [85]. However this is the first study that has reported a significant difference between unassisted and AFES-assisted MEP.

The magnitude of the difference between unassisted and AFES-assisted FVC and FEV_1 in this study was similar to the results reported by Zupan et al. [159], but smaller than in the study by Langbein et al. [85]. In addition, the magnitude of the difference between unassisted and AFES-assisted PEF was smaller in the present study compared with the study by Langbein et al. [85]. The subjects in both the current study and the study by Zupan et al. were more recently injured than the subjects studied by Langbein et al. This may explain the difference in results between the studies as recently injured patients have to relearn to coordinate their respiratory muscles [141]. On the contrary, chronically injured patients are likely to have greater atrophy of the abdominal muscles and thus benefit less from AFES than recently injured subjects. From the data available currently there is not a satisfactory explanation for the difference between the results of the current study and the study by Langbein et al. Further work will be required to fully determine the factors that influence ΔAFES.

The difference between unassisted and AFES-assisted MEP in the current study was comparable to the result reported in the single case study by Lee et al. [87]. Abdominal muscle contraction increases the intra-abdominal pressure which causes the abdominal contents to be pushed upward toward the lung and increase intra-thoracic pressure. Therefore the results reported in this study were expected.

Effect of AFES Training on AFES-Assisted Pulmonary Function Tests

The results of this study showed that AFES-assisted FVC significantly improved over the training period. In addition FEV_1, PEF and MEP all tended to increase over the training period. However, contrary to the hypothesis of this study, the difference between the unassisted and AFES-assisted outcome measures did not change over the course of the intervention. These results suggest that the improvements in AFES-assisted outcome measures were a result of the improvement in unassisted outcome measures rather than a consequence of an improvement in abdominal muscle contractile properties.

This is the first study that has specifically examined the effect of a respiratory muscle training regime on the difference between unassisted and AFES-assisted pulmonary function measures. Other studies [87, 159], have reported both unassisted and AFES-assisted outcome measures in response to respiratory muscle training but have not focussed on the difference between them. The results reported by Zupan et al. [159] appear to indicate that the differences between unassisted and AFES-assisted FVC and FEV_1 did not change following four weeks of breathing exercises, which included AFES. The results from a single case study, reported by Lee et al. [87], indicate that the difference between unassisted and AFES-assisted PEF and MEP increased after four weeks of AFES-assisted coughing exercises.

Previous work has shown that the cross sectional area of the limb muscles decreases significantly within 6 weeks post-SCI [26, 65, 128]. Although the decrease in cross sectional area is likely to vary between different muscles [26], Estenne et al. showed a decrease in the thickness of the abdominal wall muscles in chronic tetraplegic patients compared with age, sex, height and weight matched able-bodied controls [51]. In addition, Kowalski et al. [82] found a significant decrease in the weight of the abdominal muscles of cats 6 months after spinalisation. Furthermore, Kowalski et al. [82] found that the airway pressure generating capacity of the cats decreased by 46% 6 months after spinalisation. Since all of the subjects in this study were at least three months post-SCI it is presumed that their abdominal muscles would be significantly atrophied. Thus, reversing the muscle atrophy should have resulted in an increase AFES-assisted outcome measures relative to the unassisted outcome measures.

From the results of this study it is not possible to determine why the training programme did not improve the AFES-assisted outcome measures relative to the unassisted outcome measures. There are at least two possible explanations.

Firstly, The training programme was not of a sufficient duration to reverse

the effects of muscle atrophy. To the authors knowledge, there has only been one previous study in which the effects of AFES on the strength of the abdominal muscles was investigated [6]. In this study four weeks of AFES improved the force generating capacity of the abdominal muscles in able-bodied subjects. Four weeks of electrical stimulation has also been shown to improve the maximum voluntary contraction of the quadriceps muscle in able-bodied subjects [62]. However, changes in muscle contractile properties following four weeks of electrical stimulation training have been attributed to neural adaptions, rather than a morphological change in the muscle. Furthermore these neural adaptions are thought to occur at the supra spinal level [62]. Since SCI mitigates the possibility of supra spinal neural adaptions affecting abdominal muscle contraction it may be that training programs that last longer than three weeks are required before improvements in abdominal muscle contractile properties are observed in tetraplegic patients. The last statement is at least partially supported by the observation that previous FES training studies, which show an improvement in muscle strength in SCI patients, have lasted considerably longer than three weeks [11, 46].

Secondly, the design of the training programme was not suitable to induce changes in abdominal muscle strength. It is generally accepted that the most effective way to increase the strength of a muscle is to contract the muscle against a load. In comparison, repetitive unloaded contractions result in improvements in muscle endurance [79]. In the present study, AFES was applied in synchrony with a patients volitional exhalation. Therefore the abdominal muscles were unloaded relative to the abdominal muscles contracting against a held breath. Thus, it is possible that the training regime used in this study could have improved the endurance capacity rather than the strength of the abdominal muscles. The results from two previous studies support this explanation. In the first study [135], the tibialis anterior muscle of SCI patients was stimulated for two hours per day without any external loading. The results of that study showed a significant increase in the endurance capacity of the muscle but no increase in the strength of the muscle. In the second study [46], the quadriceps muscle of patients with SCI was contracted 40 times per day against a load using FES. The results of that study showed a significant increase in muscle strength.

4.4.3 Study Limitations

There was considerable intra-subject variability seen in some of the subjects. This could be attributable to fluctuating general health of the patients but might also be attributed to test-retest reliability. In this study, the mean of three attempts

which were within 20% of each other was used for analysis. This protocol was in line with ATS/ERS recommendations for the MEP test [53] but it was not possible to follow the recommendations for the FVC test [112]. Although previous work has shown ATS/ERS standards for spirometry can be applied in SCI [80] this only included subjects with chronic injuries (> 2 years). In the present study it was necessary to accept this large variation between attempts to make data collection possible as most of the subjects were in the early stages of injury and found it difficult to produce consistent results.

It is important to exercise caution when interpreting the results of this study as there is not a matched control group. Some previous work has reported that FVC, FEV_1 and PEF increase considerably within the first three months of injury due to natural recovery [86]. In another study, however, which included subjects with a similar time post injury to this study, no changes in respiratory function occurred over a period of four weeks [27]. While it is not possible to rule out natural recovery for the changes seen in this study the lack of change in respiratory function during the week before training and three weeks post training do not support this notion.

4.5 Conclusions

1. The passive AFES training programme presented in this study is a feasible technique to improve unassisted clinical respiratory measures. The results provide a basis for a future controlled trial of the technique.

2. The application of AFES acutely improves unassisted FVC, FEV_1, PEF and MEP.

3. The passive AFES training programme presented in this study is a feasible technique to improve AFES-assisted clinical respiratory measures but not AFES-assisted clinical respiratory measures relative to unassisted clinical respiratory measures. Future work with this goal should investigate the feasibility of AFES training against a resistance.

Chapter 5

Study 1: Cough Results

Coughing is an essential part of the respiratory system's defences and is required to remove secretions from the lungs. The ability to cough is severely compromised in patients with a tetraplegic SCI as a result of the paralysis of the abdominal and intercostal muscles. This puts these patients at an increased risk of developing pneumonia and atelectasis [108].

Traditional methods for the treatment of an impaired cough include postural drainage [122], mechanical insufflation-exsufflation [9] and manually assisted cough by a trained therapist [22]. However all of these methods require assistance by a trained caregiver which makes it unlikely that patients clear secretions as often as is necessary.

AFES offers a potentially new method of cough assistance in these patients [57]. Previous studies have shown that both the pressure (gastric, esophageal and mouth) and CPF are larger in AFES-assisted coughs than in unassisted coughs in tetraplegia [24, 58, 75, 87, 89, 133, 140]. A major potential advantage of AFES-assisted cough is that it could be incorporated into a device which is operated independently by the patients [57]. This would allow the patients to cough at will and thereby reduce the burden on the caregiver.

Generally AFES is applied at the end of inhalation during the glottal closure phase of the cough. Contraction of the abdominal muscles during this phase increases intrathoracic pressure, which causes a rapid expulsion of air when the glottis is opened. The more forceful the contraction of the abdominal muscles, the greater the increase in intrathoracic pressure and subsequent expiratory flow rate. It is known that by using stimulation frequency trains which include an initial high frequency burst of two to four pulses, the force production of electrically stimulated muscle can be increased compared with stimulation by CFTs. This effect is called the catchlike property of muscle and the trains that induce it

are called CITs [16]. Although CITs may be useful for maximising the efficacy of AFES-assisted cough, to date they have not been investigated for this application.

One of the consequences of SCI is considerable muscle disuse atrophy and a change in the fibre type composition of the paralysed muscles [118]. However, the effect of abdominal muscle training on AFES-assisted cough has been given limited attention [87, 104]. Prior to the start of the current study, a single case study in which the patient practiced AFES-assisted coughing for twenty minutes per day, five times a week for four weeks, found an increase in both unassisted and AFES-assisted CPF and MEP [87]. After the conclusion of the current study, the results of a fifteen patient crossover trial were published as a sequel to the single case study [104]. That study found a significant increase in unassisted and AFES-assisted CPF after six weeks of AFES-assisted cough training. These results are interesting as they suggest that an AFES cough neuroprosthesis [57] would become more effective over time.

The results described above also suggest that AFES neuromuscular training may improve unassisted cough in tetraplegia. However, AFES-assisted cough training can be considered an active training programme and is therefore subject to the disadvantages discussed in Chapter 4. The effect of an exclusive AFES passive training programme on unassisted and AFES-assisted cough has not been studied.

Leading on from previous work this study investigated the effect of a passive AFES training programme on the ability to cough. The primary aims of this study were:

1. To determine the effect of the training programme on unassisted coughing.

2. To determine the effect of the training programme on AFES-assisted cough, and on AFES-assisted cough relative to unassisted cough.

The secondary objectives of this study were:

1. To verify that AFES-assisted cough is greater than unassisted cough.

2. To determine the effect of using a CIT on AFES-assisted cough.

5.1 Methods

The study protocol and cough assessment is described in Chapter 3. In this section the methods which were specific to the analysis of the cough data are described.

The dependent outcome measures were CPF, FEV_1 and V_I. For each assessment session the means of the dependent outcome measures were taken over the best three coughs for each mode of coughing (unassisted cough, CFT cough and CIT cough). If less than three coughs were attempted for a mode of coughing then these results were excluded from the analysis.

The CFT cough outcome measures were examined as absolute values and with respect to the unassisted outcome measures (ΔCFT). Similarly, the CIT cough outcome measures were examined as absolute values, and with respect to the CFT cough outcome measures (ΔCIT-CFT) and with respect to the unassisted cough outcome measures (ΔCIT-U)

5.1.1 Primary Analysis

The changes in the dependent outcome measures over the course of the training period were investigated and compared with the changes which occurred during the control and follow up periods of the study. This analysis included only subjects who completed the final assessment session (A6) and who missed no more than one assessment session during the study. Missing data for assessment A1 was replaced by A2, missing data for assessments subsequent to A1 was replaced by the data from the previous assessment. A significant change was determined using the Friedman test with post-hoc multiple comparisons using the Tukey-Kramer Honestly Significant Difference correction.

5.1.2 Secondary Analysis

This analysis is related to the secondary objectives of this study and included all of the subjects who completed at least one of the A1 and A2 assessment sessions. For each eligible subject the magnitude of ΔCFT and ΔCIT was averaged over the baseline assessments and compared with zero using the Wilcoxon Signed Rank test.

5.2 Results

5.2.1 Stimulation timing

The automatic cough stimulation trigger was effective for the majority of subjects. The automatic trigger could not be used for subjects S3, S6, S7 and S8 as their quiet breathing and coughing peak inspiratory flows were similar. For these

subjects, stimulation was triggered manually by the researcher to coincide with the glottal closure phase of the cough.

5.2.2 Data Collection

As discussed in Chapter 3, subjects S4, S6, S13, and S16 did not complete the whole study.

The following data points were discarded since less than three coughs were recorded:

- unassisted cough on A1 for S7

- CFT cough on A1 for S4

- CIT cough on A1 for S1; on A4, A5, and A6 for S5; on A1 for S9; on A2 for S12; and on A1 for S14

CIT cough was not collected for S3, S6, S7, and S8 as the manual stimulation trigger could not be used to produce a CIT.

CFT cough was not collected for S1 or S2 because these subjects were tested using the original protocol which did not include CFT cough (see Chapter 3 for details).

As a result of the missing data described above different groups of subjects were used for different parts of the analysis. These are described in Table 5.1.

5.2.3 Forced Exhaled Volume in One Second

For the majority of subjects the exhalation time of a cough was shorter than one second and it was not possible to calculate FEV_1. Example flow rate traces of coughs from S5 and from S15 are shown in Figure 5.1. S5 was the only subject for which the exhalation time of cough was consistently greater than one second. Accordingly, FEV_1 was removed as an outcome measure from the analysis.

Table 5.1: Subjects used for different parts of the cough analysis. N indicates the number of subjects that were included in each part of the analysis.

Analysis	Description	N	Subjects
Baseline CFT Cough	Subjects who completed at least one baseline assessment (A1 and A2) for both unassisted cough and CFT cough	14	S3 to S16
Baseline CIT Cough	Subjects who completed at least one baseline assessment for unassisted cough, CFT cough and CIT cough	10	S4, S5, S9 to S16
Training Unassisted Cough	Subjects who completed the study and missed no more than one unassisted cough assessments	12	S1 to S3, S5, S7 to S12, S14, S15
Training CFT Cough	Subjects who completed the study and missed no more than one of the unassisted cough and CFT cough assessments	10	S3, S5, S7 to S12, S14, S15
Training CIT Cough	Subjects who completed the study and missed no more than one of the unassisted cough, CFT cough and CIT cough assessments	6	S9 to S12, S14, S15

(a) S5, A2   (b) S15, A2
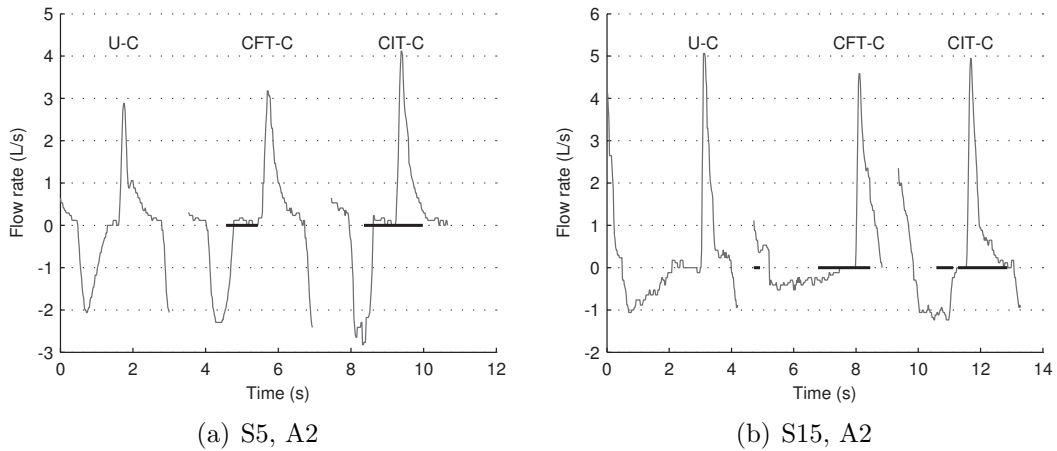
Figure 5.1: Example flow rate traces of unassisted cough, CFT cough, and CIT cough for (a) S5 during A2, for which it was possible to calculate FEV_1 and (b) S15 during A2, for which it was not possible to calculate FEV_1. The bold black line shows when stimulation was applied.

5.2.4 Unassisted Cough

The unassisted cough results are shown for the *Training Unassisted Cough* subjects in Figure 5.2 and summarised in Table 5.2. The standard deviations in Table 5.2 and the individual subject data in Figure 5.2 demonstrate that there was considerable variation for all outcome measures both between subjects and within individual subjects.

The longitudinal change in CPF and V_I were found to be statistically significant according to the Friedman test. Multiple comparison testing found a significant difference between A2 and A5 for the CPF results and between A2 and A5 for the V_I results.

(a)

(b)
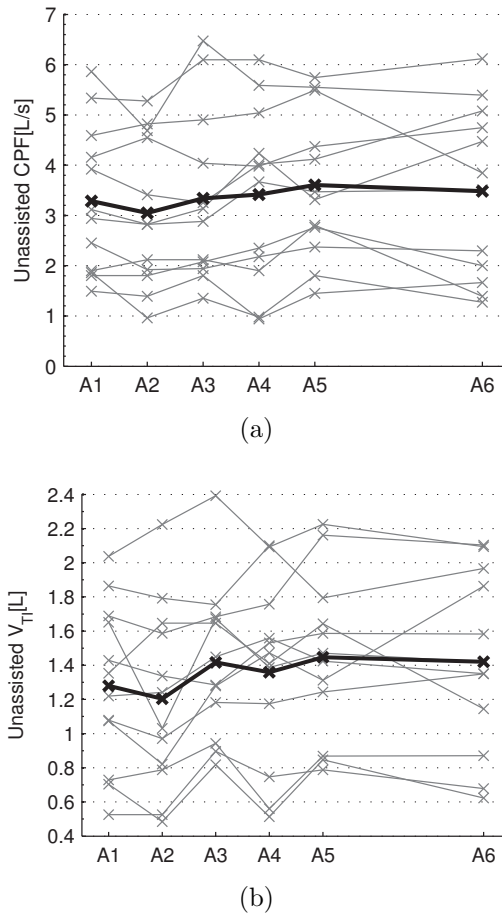
Figure 5.2: Unassisted cough results over the whole study. Individual subject results are represented by the grey lines while the group mean is shown by the bold black line.

Table 5.2: Mean (standard deviation) unassisted cough results for each outcome measure shown for each assessment session. χ^2 is the Friedman test statistic and p is the corresponding p-value.

	A1	A2	A3	A4	A5	A6	χ^2	p
CPF (L/s)	3.29 (1.47)	3.05 (1.48)	3.34 (1.70)	3.42 (1.73)	3.60 (1.47)	3.48 (1.71)	12.14	0.033
V_I (L)	1.28 (0.48)	1.20 (0.53)	1.42 (0.45)	1.36 (0.53)	1.45 (0.48)	1.42 (0.52)	17.36	0.004

5.2.5   AFES-Assisted Cough at Baseline

CFT Cough

Flow rate traces from example coughs are shown for S16 and S14 in Figure 5.3. This figure shows that CPF was considerably higher during both CFT cough and CIT cough, compared with unassisted cough, for S16. Conversely, CPF was substantially smaller during CFT cough and CIT cough, compared with unassisted cough, for S14.

(a) S16, A1   (b) S14, A2
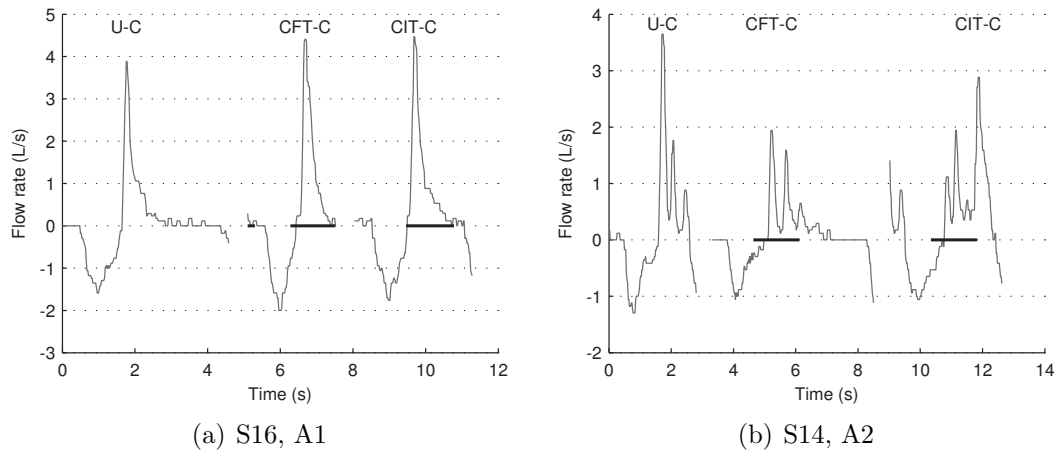
Figure 5.3: Flow traces of the best unassisted cough, CFT cough, and CIT cough from (a) S16 on A1 who had the largest CFT cough in comparison to unassisted cough and (b) S14 on A2 who had the smallest CFT cough in comparison with unassisted cough. The bold black line shows when stimulation was applied. U-C: unassisted cough; CFT-C: CFT cough; CIT-C: CIT cough.

Table 5.3 shows the group mean unassisted cough, CFT cough and ΔCFT cough averaged baseline results for the *Baseline CFT Cough* subjects. ΔCFT cough was not significantly different from zero for either CPF (p=0.14) or V_I (p=0.81). The repeatability of ΔCFT cough was poor across A1 and A2; CPF was only consistently positive for five out of the twelve subjects who completed both assessment sessions.

Table 5.3: The group mean (standard deviation) CFT cough results at baseline. Baseline data was calculated by taking the mean over A1 and A2 for each subject. p is the probability that ΔCFT cough is equal to zero which was calculated using the Wilcoxon Signed Rank test. U-C: unassisted cough; CFT-C: CFT cough; ΔCFT-C: ΔCFT cough.

	U-C	CFT-C	ΔCFT-C	p
CPF (L/s)	2.88 (1.36)	2.99 (1.41)	0.16 (0.48)	0.14
V_I (L)	1.11 (0.41)	1.10 (0.44)	-0.00 (0.15)	0.81

Figure 5.4 shows the results of the regression of CPF on V_I for unassisted cough and CFT cough. The regression found CPF to vary significantly with respect to V_I for both unassisted cough and CFT cough (p=0.001 and p=0.012, respectively). However, there was no evidence to suggest that CPF was different between CFT cough and unassisted cough after adjusting for the variability in V_I.
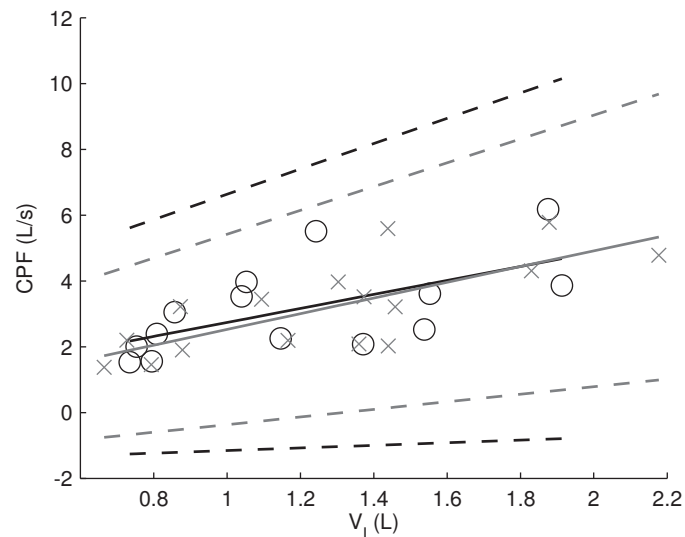
Figure 5.4: Fit from least squares regression of CPF on V_I for unassisted cough (grey lines and markers) and CFT cough (black lines and markers). The regression was done using the mean V_I and CPF over all assessment sessions for each subject. The solid lines represent the fitted model and the dashed lines represent the confidence intervals of the fit. The Durbin-Watson test found the residuals from the unassisted cough and CFT cough fits to meet the assumption of random error (p=0.103 and p=0.081, respectively).

CIT Cough

Table 5.4 shows the group mean baseline results for the *Baseline CIT Cough* subjects. ΔCIT-CFT was not significantly different from zero for either CPF (p=0.27) or V_I (p=0.92). ΔCIT-CFT CPF was consistently positive across A1 and A2 for one out of the six subjects who completed both assessment sessions. ΔCIT-U was not significantly different from zero for either CPF (p=0.43) or V_I (p=0.84). ΔCIT-U CPF was consistently positive across A1 and A2 for three out of the seven subjects who completed both assessment sessions.

Table 5.4: The group mean (standard deviation) results for the CIT cough subjects at baseline. Baseline data was calculated by taking the mean over A1 and A2 for each subject. U-C: unassisted cough; CFT-C: CFT cough; CIT-C: CIT cough; ΔCIT-U-C: ΔCIT-U cough; ΔCIT-CFT-C: ΔCIT-U cough

	U-C	CFT-C	CIT-C	ΔCIT-U-C	ΔCIT-CFT-C
CPF (L/s)	3.29 (1.41)	3.28 (1.57)	3.44 (1.40)	0.17 (0.54)	0.10 (0.36)
V_I (L)	1.19 (0.39)	1.11 (0.45)	1.16 (0.45)	-0.00 (0.14)	0.02 (0.10)

5.2.6 Effect of Training on AFES-assisted Cough

CFT Cough

The CFT cough results for the *Training CFT Cough* subjects are summarised in Table 5.5 which show a pattern similar to that of the unassisted cough. There was considerable variation, both inter and intra subject, for each of the outcome measures. CPF tended to increase over the training phase but this change was not statistically significant. The change in V_I was statistically significant over the course of the study according to the Friedman test. Multiple comparison testing found significant differences between A1 and A5, and between A1 and A6.

The group mean CFT cough and unassisted cough results for the *Training CFT Cough* subjects are shown in Figure 5.5. The figure shows that the difference between unassisted cough and CFT cough does not change throughout the study for either CPF or V_I. This observation is reflected in Table 5.6 which shows that neither ΔCFT cough CPF nor V_I changed significantly during the course of the study.

Table 5.5: Group mean (standard deviation) results for CFT cough over the course of the study. χ^2 is the Friedman test statistic and p is the corresponding p-value.

	A1	A2	A3	A4	A5	A6	χ^2	p
CPF (L/s)	3.08 (1.58)	3.09 (1.70)	3.25 (1.85)	3.16 (1.78)	3.47 (1.57)	3.47 (1.71)	9.04	0.108
V_I (L)	1.10 (0.37)	1.16 (0.52)	1.29 (0.42)	1.25 (0.49)	1.39 (0.50)	1.32 (0.46)	16.95	0.005

Table 5.6: Group mean (standard deviation) results for ΔCFT cough over the course of the study. χ^2 is the Friedman test statistic and p is the corresponding p-value.

	A1	A2	A3	A4	A5	A6	χ^2	p
CPF (L/s)	-0.03 (0.44)	0.20 (0.77)	0.03 (0.24)	-0.06 (0.63)	0.05 (0.49)	0.03 (0.53)	3.98	0.552
V_I (L)	-0.08 (0.17)	0.07 (0.21)	-0.05 (0.12)	-0.02 (0.20)	0.04 (0.15)	-0.02 (0.27)	5.65	0.342
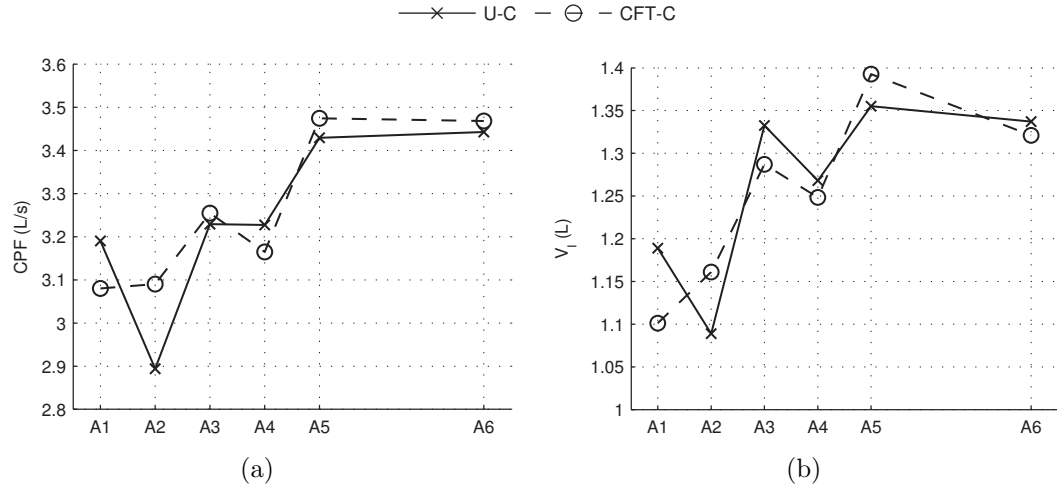
Figure 5.5: The changes in CFT cough and unassisted cough, CPF and V_I means throughout the study. U-C: unassisted cough; CFT-C: CFT cough

CIT Cough

The CIT cough results for the *Training CIT Cough* subjects are summarised in Table 5.7. As with the unassisted cough results and the CFT cough results the inter and intra subject variation was considerable for both CPF and V_I. The table shows that both CPF and V_I tended to increase over the training intervention. The statistical analysis found that these trends were not statistically significant.

The group mean CIT cough, CFT cough, and unassisted cough results for the *Training CIT Cough* subjects are shown in Figure 5.6. The figure shows that the difference between CIT cough and both unassisted cough and CFT cough did not change throughout the study for either CPF or V_I. This observation is reflected in Tables 5.8 and 5.9 which show that the ΔCIT-CFT cough and ΔCIT-U cough outcome measures did not change significantly throughout the study.

Table 5.7: Group mean (standard deviation) results for CIT cough results over the course of the study. χ^2 is the Friedman test statistic and p is the corresponding p-value.

	A1	A2	A3	A4	A5	A6	χ^2	p
CPF (L/s)	3.65 (1.50)	3.76 (1.52)	3.84 (1.85)	3.77 (1.70)	4.07 (1.70)	3.98 (1.67)	7.07	0.215
V_I (L)	1.38 (0.54)	1.43 (0.57)	1.50 (0.52)	1.43 (0.54)	1.59 (0.50)	1.52 (0.46)	3.15	0.678

Table 5.8: Group mean (standard deviation) results for ΔCIT-CFT cough over the course of the study. χ^2 is the Friedman test statistic and p is the corresponding p-value.

	A1	A2	A3	A4	A5	A6	χ^2	p
CPF (L/s)	0.20 (0.64)	0.03 (0.45)	-0.11 (0.25)	0.04 (0.63)	-0.03 (0.18)	-0.02 (0.38)	3.23	0.665
V_I (L)	0.05 (0.14)	0.01 (0.20)	-0.06 (0.14)	-0.02 (0.15)	-0.02 (0.09)	0.05 (0.12)	4.20	0.521
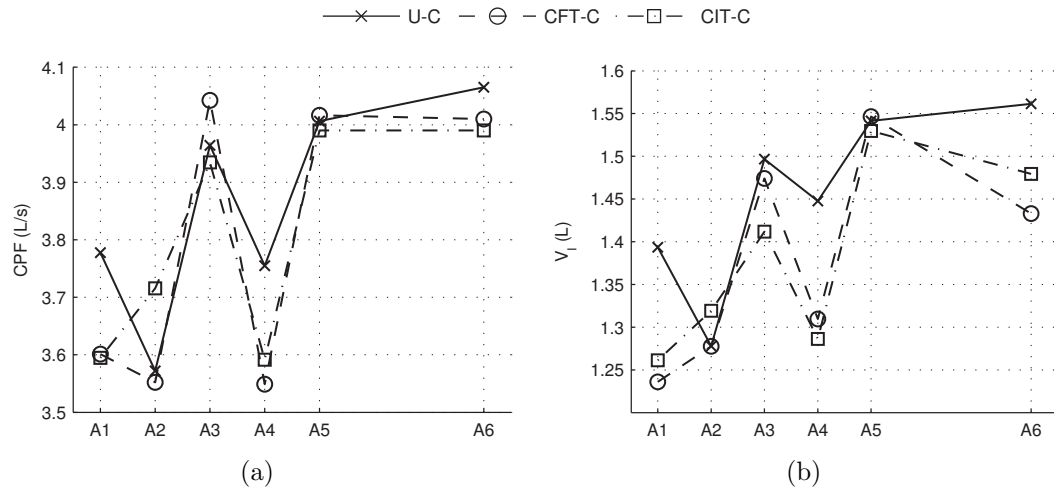
Figure 5.6: The changes in unassisted cough, CFT cough and CIT cough, CPF and V_I means throughout the study. U-C: unassisted cough; CFT-C: CFT cough; CIT-C: CIT cough.

Table 5.9: Group mean (standard deviation) results for ΔCIT-U cough over the course of the study. χ^2 is the Friedman test statistic and p is the corresponding p-value.

	A1	A2	A3	A4	A5	A6	χ^2	p
CPF (L/s)	-0.05 (0.60)	0.19 (0.54)	-0.06 (0.32)	-0.09 (0.56)	-0.01 (0.62)	0.04 (0.55)	3.72	0.591
V_I (L)	-0.06 (0.21)	0.04 (0.15)	-0.09 (0.16)	-0.11 (0.16)	-0.06 (0.16)	-0.11 (0.18)	6.68	0.245

5.3 Discussion

The primary aim of this study was to investigate the effect of a passive abdominal muscle training program on unassisted and AFES-assisted cough. The secondary aims of this study were to verify the results of previous authors that AFES-assisted cough was greater than unassisted cough and to evaluate the use of a CIT to improve the effectiveness of AFES-assisted coughing. This study found that unassisted, but not CFT cough or CIT cough, CPF was significantly augmented over the training period. Neither CFT cough nor CIT cough significantly improved unassisted CPF prior to training.

5.3.1 Unassisted Cough

The results of this study found that there was a progressive increase in the group mean of both unassisted CPF (18%) and V_I (21%) over the training period (between A2 and A5). While this was statistically significant there was a decrease in both measures in the control period (A1 to A2) reducing the overall difference between A1 and A5 to approximately 9% and 13% respectively. There was however a consistent trend that suggests a training effect. There was a small

decrease through the follow up period (between A5 and A6), but there appeared to be some residual benefit. This is similar to the change in PEF and FVC shown in Chapter 4.

The tetraplegic patients in this study were unable to contract their abdominal muscles voluntarily and so it is unlikely that CPF improved through an increase in abdominal muscle strength. Instead, since lung recoil force becomes greater with increasing lung volume, the most likely explanation is that CPF increased as a result of increased V_I. This relationship between CPF and V_I was demonstrated by the regression of CPF on V_I using the results of this study.

There are two possible explanations for the increase in V_I observed over the training period:

1. Patients exerted greater effort in the later training sessions. While this explanation cannot be eliminated, since V_I was not explicitly controlled for, it should be noted that patients were encouraged by the researcher to cough with maximum effort throughout the study.

2. It was less strenuous for patients to take larger inhalations as a result of increased inhalation capacity. This explanation is coherent with the findings of Chapter 4 which showed that FVC increased during this training programme.

Previous work has reported the effects of an AFES-assisted cough training programme on unassisted cough in tetraplegia [87, 104]. The results of these studies showed that unassisted CPF increased by 23% [87] and by 19% [104] after three and six weeks of training respectively. These increases are similar to the increase in CPF between A2 and A5 reported in the current study. Although these studies used a different AFES training modality to the current study, the results further suggest that AFES neuromuscular training is a useful tool to improve unassisted cough in tetraplegia.

5.3.2 AFES-Assisted Cough

In this study AFES-assisted cough was tested using both a CFT stimulation pattern, the standard method used for AFES-assisted cough, and a CIT stimulation pattern, a new method which has the potential to enhance the efficacy of AFES-assisted cough. The main findings of this study were:

1. At baseline, the CFT cough and the CIT cough outcome measures were not different from unassisted cough outcome measures, and the CIT cough outcome measures were not different from CFT cough outcome measures.

2. The absolute values of the CFT cough and the CIT cough outcome measures tended to improve over the training period but this change was not significant.

3. AFES training did not affect the CFT cough outcome measures relative to the unassisted cough outcome measures nor did it affect the CIT cough outcome measures relative to either the CFT cough outcome measures or the unassisted cough outcome measures.

Baseline CFT cough

The results showed only a small increase between the group mean unassisted cough and CFT cough CPF, which was not statistically significant. Furthermore, ΔCFT cough was not consistent over A1 and A2 for more than half of the subjects studied.

These results are contrary to the original hypothesis of this study. The application of AFES to the otherwise paralysed abdominal wall muscles during the glottal closure phase of a cough should augment the intrathoracic pressure that the patient can generate volitionally. In turn, this increased intrathoracic pressure should result in a CPF greater than that with the patient's volitional effort.

There are at least two possible explanations for the results of this study.

1. AFES did not augment unassisted intrathoracic pressure. While this explanation cannot be eliminated since intrathoracic pressure was not measured, a strong visual contraction of the abdominal muscles in response to AFES was observed in every subject who participated in this study. Furthermore, the results of Chapter 4 showed, in the same group of subjects, that AFES-assisted MEP and PEF were greater than unassisted MEP and PEF. Therefore, it seems unlikely that the lack of difference between unassisted cough and CFT cough can be explained by insufficient abdominal muscle contraction.

2. The timing of stimulation affected the coordination of the subjects' other respiratory muscles during cough. In this study stimulation was timed automatically to coincide with the glottal closure phase of the cough for the majority of the subjects tested. This method was devised by Gollee et al. [57, 58] who showed it to be effective at improving unassisted CPF in chronically injured tetraplegic patients. A cough consists of a complex series of muscle contractions which have to be timed appropriately. In addition, patients in the post-acute stage of injury are relearning to coordinate their

muscles [141]. Although an automatic method of applying AFES should provide consistency, its timing is based on a single measurement. Therefore, particularly for the subjects included in this study, it is possible that the automatic method would not be as effective as a human operator in sensing the best timing for coughing. Furthermore, it is possible that inappropriately timed abdominal contraction could perturb the coordination of the other respiratory muscles during cough.

The results of this study contradict the results found by several previous authors [24,58,75,87,89,104,140]. There has been only one previous study which has not found a difference between unassisted and CFT CPF [133]. Although there are several methodological differences between the current study and previous studies, the major differences are:

1. The time post injury. The average duration post injury for subjects in the previous studies ranged between 21 months [58] to 11.9 years [104] whereas the average duration post injury for the subjects in the current study was 13 months. As more recently injured subjects in the current study are likely to be in the process of relearning to coordinate their breathing muscles this could affect the outcome of AFES and explain the contradictions between the results of this study and previous studies.

2. The difference in stimulation frequency. The stimulation frequency in this study was set at 30 Hz whereas most previous studies have used 50 Hz [24, 58, 75, 87, 89]. In this study the cough stimulation frequency was chosen to match the stimulation frequency that was used during AFES training, which was conducted at 30 Hz to minimize the impact of muscle fatigue during the training sessions. It is known that the force of contraction progressively increases with the frequency of stimulation. In addition, DiMarco et al. [39] demonstrated that the airway pressure during SCS at 30 Hz was 80% of the pressure generated when the stimulation frequency was set at 50 Hz. Although the difference in stimulation frequency could have explained a reduced CFT CPF compared with other studies, the author does not believe that the lack of difference between unassisted and CFT CPF was a result of insufficient contraction of the abdominal muscles (discussed above).

The Effect of AFES Training on CFT Cough

The results of this study showed an increase in CFT CPF over the training phase which was not statistically significant. The results also showed the ΔCFT CPF

did not change throughout the study. This indicates that any change in CFT CPF was a consequence of the change in unassisted CPF.

The results do not support the hypothesis of this study that AFES training would augment ΔCFT cough by reversing the atrophy of the abdominal muscles which occurs after a SCI. The explanations for this finding are:

1. This study did not find a difference between CFT cough and unassisted cough at baseline (the reasons for this were discussed previously). Accordingly training would not improve one more than the other.

2. The training programme was not long enough to reverse the atrophy of the abdominal muscles. This was discussed in Chapter 4.

3. The training system affected the respiratory system but this effect was not useful for AFES-assisted cough. Following a tetraplegic SCI there is both a reduction in the abdominal muscle bulk and a shift in the fibre composition of muscles. Although not demonstrated in the abdominal muscles, previous studies have shown that in the vastus laterallis muscles of a patient with SCI there is a reduction in type IIa fibres and an increase in type IIx fibres [26]. The reduced cross sectional area of the abdominal muscle fibres would relate to a reduction in maximum force production of the muscle, which is undesirable for an AFES-assisted cough. The fibre type transformation would reduce the contraction time of the muscle and increases the force generated per fibre cross sectional area, which is an advantage for AFES-assisted cough. The training modality did not train the abdominal muscles against a resistance, which, according to the overload principle of exercise training, is a key component of improving the strength of a muscles. Therefore, it is possible that the AFES training program reversed the shift in muscle fibre composition without reversing the atrophy of the abdominal muscles, which would result in a diminished effect on ΔCFT cough.

There has been a single case study [87] and a follow up fifteen patient crossover trial [104] that have investigated the effect of practicing AFES-assisted cough over a period of several weeks on AFES-assisted cough in tetraplegia. The results of the crossover trial showed that AFES-assisted CPF increased by 17%, but that ΔCFT CPF did not change, during the training programme. In addition, this study did not find a change in abdominal muscle strength through the training programme, suggesting that the change in AFES-assisted CPF was a result of underlying changes in unassisted CPF. There are several important comparisons that can be made with the current study. In the crossover study:

1. AFES was applied during the glottal closure phase of a cough. Compared with the current study, this would have provided a greater resistance against the contracting abdominal muscles, which may have stimulated a greater training response.

2. There were 50 abdominal muscle contractions per training session in the crossover trial. Compared with the current study, which included an average of 600 abdominal muscle contractions per training session[1], this would have reduced the training response.

3. The training programme allowed the patient to practice AFES-assisted cough as well as training the abdominal muscles. Coughing requires a series of co-ordinated muscle contractions which like any skill could be expected to improve with practice.

The crossover study, like the current study, did not include any measurements of abdominal muscle thickness, abdominal fiber type composition, or respiratory muscle coordination, and therefore it is unclear what effect AFES training has on AFES-assisted cough. Investigation of these aspects should help to further determine the potential of AFES training to improve AFES-assisted cough and allow future training paradigms to be optimised for this application.

CIT Cough

The results of this study showed that at baseline there was no difference between CIT cough and both CFT cough and unassisted cough. During the training period CIT cough tended to increase but this increase was not statistically significant. ΔCIT-CFT cough and ΔCIT-U cough did not change during the training period suggesting that any change in CIT cough was a consequence to the change in unassisted cough. These results were contrary to the hypothesis of this study, which was that a CIT would augment the contractile force of the abdominal muscles, and in turn CPF, compared with a CFT.

This was the first study to investigate the difference between CFT cough and CIT cough. The hypothesis was based on previous studies which have shown in animals and in human quadriceps muscles, that the maximum force produced and rate of force production is greater when using a CIT [16]. The same explanations apply to the CIT cough results as those discussed for CFT cough. One further

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[1]Assuming a breathing rate of fifteen breaths per minute and a forty minute training session duration

reason, which applies only to CIT cough, is that a CIT does not affect the abdominal muscles in the same way as it affects the quadriceps muscle group. Further work, including measurement of gastric pressure is required to understand the effect of a CIT on AFES-assisted cough.

5.4 Study Limitations

There was a high degree of inter and intra subject variability observed in the results of this study. There are two potential sources that may have contributed to this variability: (i) cough inhalation volume, which is an important factor in CPF; and (ii) the fluctuating general health of this group of recently injured patients.

5.5 Conclusions

1. The passive AFES training programme presented in this study is a feasible technique to improve unassisted CPF in tetraplegia. The results provide the basis for a future controlled trial of the technique.

2. The CFT and CIT cough results should be verified in a repeat study. The baseline CFT cough results in this study contradicted the results of at least six previous studies. The author believes that inhalation volume, stimulation timing, stimulation frequency and the time post injury of subjects may explain this contradiction and recommends that a follow up study should aim to investigate the relationship between these factors and CFT CPF. A follow up study is also recommended to investigate the effect of passive AFES training on tetraplegic patients whose AFES-assisted CPF is greater than unassisted CPF at baseline.

Chapter 6

Study 1: Quiet Breathing

6.1 Introduction

In tetraplegic patients who are still able to breathe spontaneously, V_T during resting breathing has been shown to be significantly lower than in the able-bodied population [18]. In some patients the reduced V_T is compensated for by an increase in BR resulting in a $\dot{V}$ that is similar to the able-bodied population. In other patients BR is similar or reduced, and thus $\dot{V}$ is reduced, compared with the able-bodied population [18]. Maximum voluntary ventilation is also considerably lower in patients with tetraplegia (78 L/min [109]) compared with able bodied controls (140-160 L/min [79]). These alterations in respiratory physiology in tetraplegia may contribute to dyspnea [23], incidence of atelectasis [23, 154] and likelihood of acute respiratory failure [154]. New treatments which can improve ventilation in these patients are highly important.

AFES applied during exhalation has previously been shown to improve ventilatory parameters in healthy subjects [132, 134], in tetraplegic patients who could breathe spontaneously [57, 58, 134] and in tetraplegic patients who required MV [78]. These previous studies have identified the potential of using AFES to improve ventilation. There remain several important aspects of this technique which should be studied:

1. The temporal response of the ventilatory parameters during an extend period of AFES-assisted breathing. In all of the previous studies the effect of AFES-assisted breathing has been studied by comparing mean ventilatory parameters between unassisted and AFES-assisted breathing. The disadvantage of this approach is that temporal changes in ventilatory breathing parameters during AFES-assisted breathing would not be detected.

2. The effect of AFES-assisted breathing on blood gas levels. Gollee et al. [58] observed that AFES-assisted breathing reduced ET_{CO_2} in two out of four tetraplegic patients and postulated that the increased ventilation induced by AFES offset the increase in metabolic demand resulting from contraction of the abdominal muscles. Since the study by Gollee et al. only included a limited number of patients, this observation should be verified in a larger patient group.

3. The effect of an abdominal muscle training programme on AFES-assisted breathing. The atrophy of skeletal muscle following a SCI is well documented in several muscle groups including the abdominal muscles [51]. It is reasonable to assume that a reversal of abdominal muscle atrophy would result in an improvement in the ventilatory benefits gained from AFES-assisted breathing.

The results presented in Chapter 4, as well as the findings by other authors [27,159], have shown that an AFES based respiratory muscle training programme can improve unassisted FVC in tetraplegia. It is possible that an increase in FVC would allow a patient to breathe more efficiently, by taking slower deeper breaths, and reduce dyspnea in patients with severely compromised V_T.

6.1.1 Aims

Leading on from previous work this study had the following aims:

1. To characterise the temporal response of ventilatory and blood-gas measurements during extended periods of AFES-assisted breathing.

2. To determine whether three weeks of AFES abdominal muscle training affects the respiratory system response to AFES-assisted breathing.

3. To determine whether the training programme affects unassisted ventilatory and blood-gas measurements.

6.2 Methods

The study protocol and quiet breathing assessment is described in Chapter 3. In this section the analysis methods specific to the quiet breathing data are described.

The test protocol included three periods in the following order: i) one minute of unassisted breathing; ii) five minutes of AFES-assisted breathing; and iii) one minute of unassisted breathing. As described in Chapter 3, the first three subjects (S1, S2, and S3) recruited for the study completed a different protocol. These subjects completed three minutes of unassisted breathing followed by ten minutes of AFES-assisted breathing and did not complete a period of unassisted breathing after AFES-assisted breathing. In the analysis of these subjects' data only the final minute of unassisted breathing and the first five minutes of AFES-assisted breathing were included.

6.2.1 Analysis

The dependent outcome measures were V_T, BR, $\dot{V}$, ET_{co_2} and $T_{I/TOT}$.

Quiet Breathing Regions

In each assessment session the seven minutes of quiet breathing were discretised into four regions. The four regions are illustrated in Figure 6.1(a) and described as follows:

1. **Unassisted-QB**: The last sixty seconds of unassisted breathing which occurred before the start of AFES-assisted breathing.

2. **AFES-start**: The first sixty seconds of AFES-assisted breathing.

3. **AFES-end**: The last sixty seconds of AFES-assisted breathing.

4. **post-AFES**: The first sixty seconds of unassisted breathing which occurred after the AFES-assisted breathing had finished.

In selecting the data included in each quiet breathing region, windows of sixty seconds of breathing data were selected by working from the transition between unassisted and AFES assisted breathing until the cumulative sum of the selected breaths' period was greater than sixty seconds. For example to select the unassisted-QB data, working back from the point where AFES started, the breathing period of individual breaths were cumulatively summed until the total was greater than sixty seconds. In cases where sixty seconds worth of breathing data were not available all suitable breaths in a region were extracted.
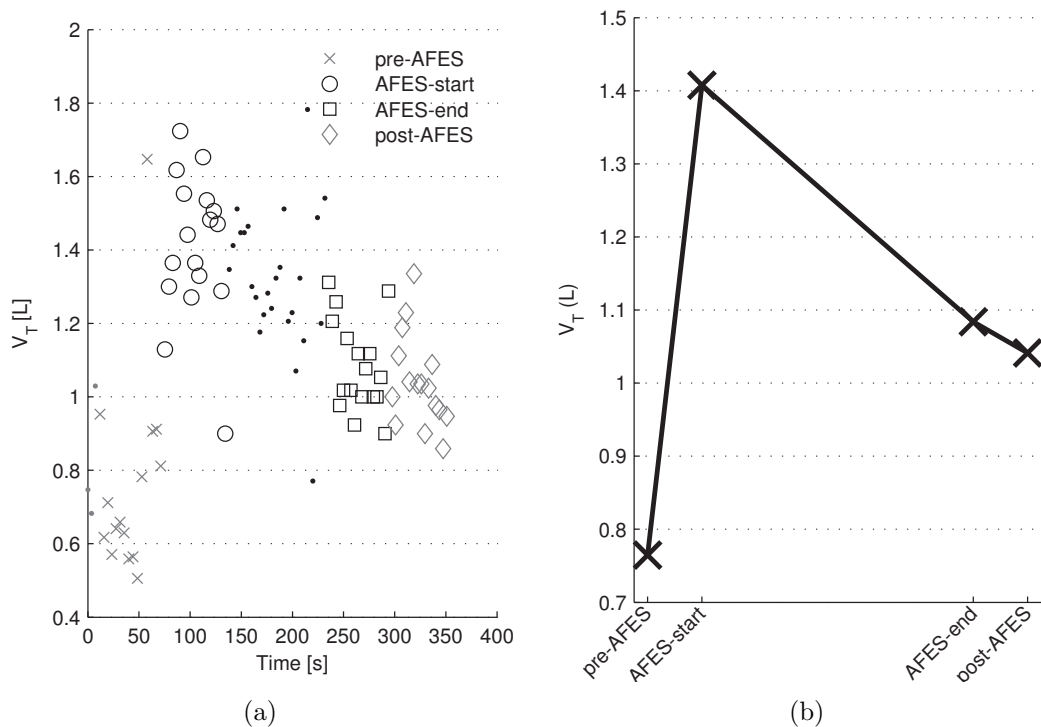
Figure 6.1: The effect of dividing the quiet breathing test into four discrete regions. (a) shows the original breath by breath tidal volume data for S18 on A1 as a function of time. In (a) the four regions of the quiet breathing test have been marked using crosses, circles, squares and diamonds. The single dots represent breaths that were not part of the regions used in the analysis. In (b) the quiet breathing data represented using the mean at each region is shown. As can be seen from the figure, by defining four regions of interest in the quiet breathing test, the time series data can be summarised using four numbers while still maintaining the main features of the data.

Baseline Analysis

The purpose of the baseline analysis was to investigate the temporal change in ventilatory parameters during AFES-assisted breathing at baseline (i.e. aim one). The baseline analysis included all sixteen subjects recruited and was completed using the data collected at A2 since every subject completed this assessment session. The group mean outcome measure at each region was compared. In addition, the ET_{CO_2} profiles of AFES responder subjects were examined. Given that V_T is the most direct measure of the effect of AFES on the respiratory system, responder subjects were defined as those whose V_T increased between unassisted-QB and AFES-start.

Training Analysis

The purpose of the training analysis was to determine the effect of the three week AFES training programme on AFES-assisted and unassisted breathing parameters (i.e. aims two and three). This analysis included the twelve subjects who completed the study (S4, S6, S13, and S6 withdrew prematurely from the study, see Chapter 3).

Statistics

Pooled results were tested to see whether they followed a normal distribution using the Shapiro-Wilks test. Since no evidence to suggest that the data followed a non-normal distribution was found, all statistical comparisons were performed using parametric tests. Paired comparisons were performed using the paired t-test. Intra subject comparisons of three or more groups were performed using the repeated measures Analysis of Variance (ANOVA). Post-hoc multiple comparison testing using the Tukey-Kramer Honestly Significant Difference criterion was used when a significant difference was detected by the ANOVA. The statistical significance level was set at $p < 0.05$.

6.3 Results

AFES-assisted quiet breathing was well tolerated and the subjects did not have any problems following the protocol.

There were technical issues on several of the assessment sessions that resulted in incomplete data sets. The most commonly occurring issue was for the capnograph not to be turned on for the assessment session. As a result, ET_{CO_2} data was not collected for: S4 on A1 and A2; S6 on A3; S7 on A3; and S9 on A1. A software problem during A1 for S12 meant that it was not possible to test AFES-assisted breathing. This resulted in only pre-AFES data being available on A1 for this subject. A second technical issue was that the spirometer would stop recording occasionally for short periods. If this was greater than thirty seconds then the test was repeated.

6.3.1 The Baseline Response of the Respiratory System to AFES-Assisted Breathing

Figure 6.2 shows the change in the dependent outcome measures during the quiet breathing test at A2. In the plots, the light gray lines represent individual subjects

and the black line represents the overall group mean.
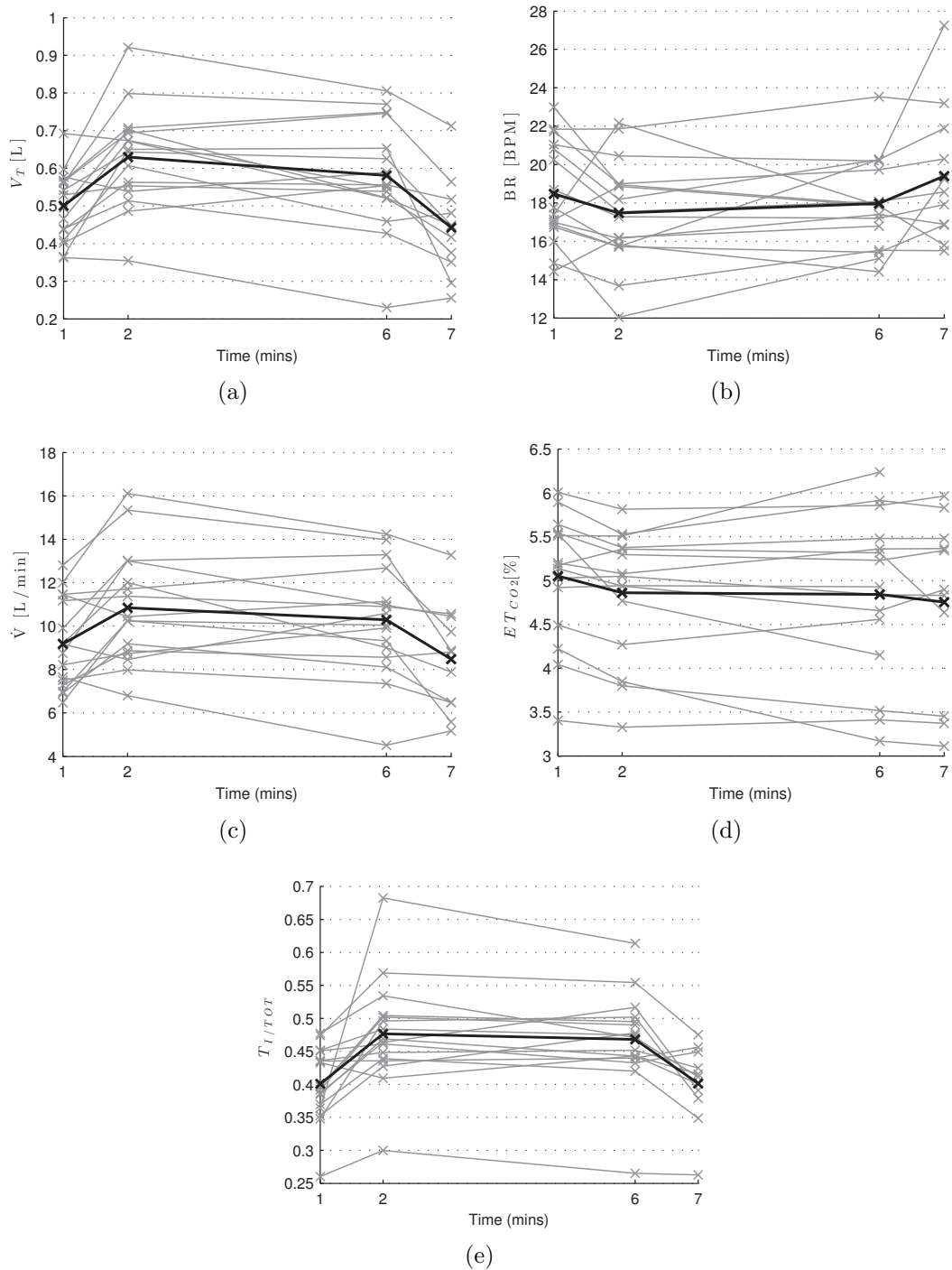
Figure 6.2: Results of the quiet breathing test on A2 for the baseline subjects. The gray lines in each plot represent individual subjects and the thick black line represents the overall group mean.

Analysis of the Whole Group

There was a similar trend for the group mean V_T, $\dot{V}$ and $T_{I/TOT}$: there was an increase between unassisted-QB and AFES-start, followed by a slight decrease between AFES-start and AFES-end and a further decrease between AFES-end and post-AFES. A statistically significant change during this trend was found for V_T, $\dot{V}$, and $T_{I/TOT}$ (all p<0.001); post-hoc multiple comparison testing found a significant difference from unassisted-QB to AFES-start and AFES-end; and from AFES-start and AFES-end to post-AFES.

The group mean BR and ET_{CO_2} both decreased between unassisted-QB and AFES-start and increased between AFES-start and AFES-end. The group mean BR increased between AFES-end and post-AFES whereas the group mean for ET_{CO_2} decreased. Statistical testing did not find a significant difference between any of the quiet breathing test regions for both BR (p=0.089) and ET_{CO_2} (p=0.061).

ET_{CO_2} Analysis

As shown in Figure 6.2, the individual subjects' responses for V_T, $\dot{V}$ and $T_{I/TOT}$ were similar whereas their responses for BR and ET_{CO_2} were mixed.

There were thirteen responder subjects whose V_T increased between unassisted-QB and AFES-start. Of these subjects ET_{CO_2} decreased between unassisted-QB and AFES-start for eleven subjects, increased for one subject (S7) and was not recorded for one subject (S4). S7 had the smallest change in V_T between unassisted-QB and AFES-start.

ET_{CO_2} decreased between AFES-start and AFES-end for six of the responder subjects (Group A in Table 6.1, page 125) and increased for six of the responder subjects (Group B in Table 6.1). The response profiles of Group A and Group B are shown in Figure 6.3. The difference between unassisted-QB and AFES-start was significant between the two groups for V_T ($p = 0.018$), but not for $\dot{V}$ ($p = 0.13$), BR ($p = 0.36$), ET_{CO_2} ($p = 0.10$) or $T_{I/TOT}$ ($p = 0.41$). The change between AFES-start and AFES-end was significantly different between the two groups for ET_{CO_2} ($p < 0.001$), but not for V_T, $\dot{V}$, BR or $T_{I/TOT}$. Table 6.1 shows the demographic data of both groups, which were found to be similar. The one noticeable difference was the mean time post injury which was considerably greater in Group A compared with Group B. It should be noted that Group A contained the two chronically injured subjects that completed this study.

(a)

(b)

(c)

(d)

(e)
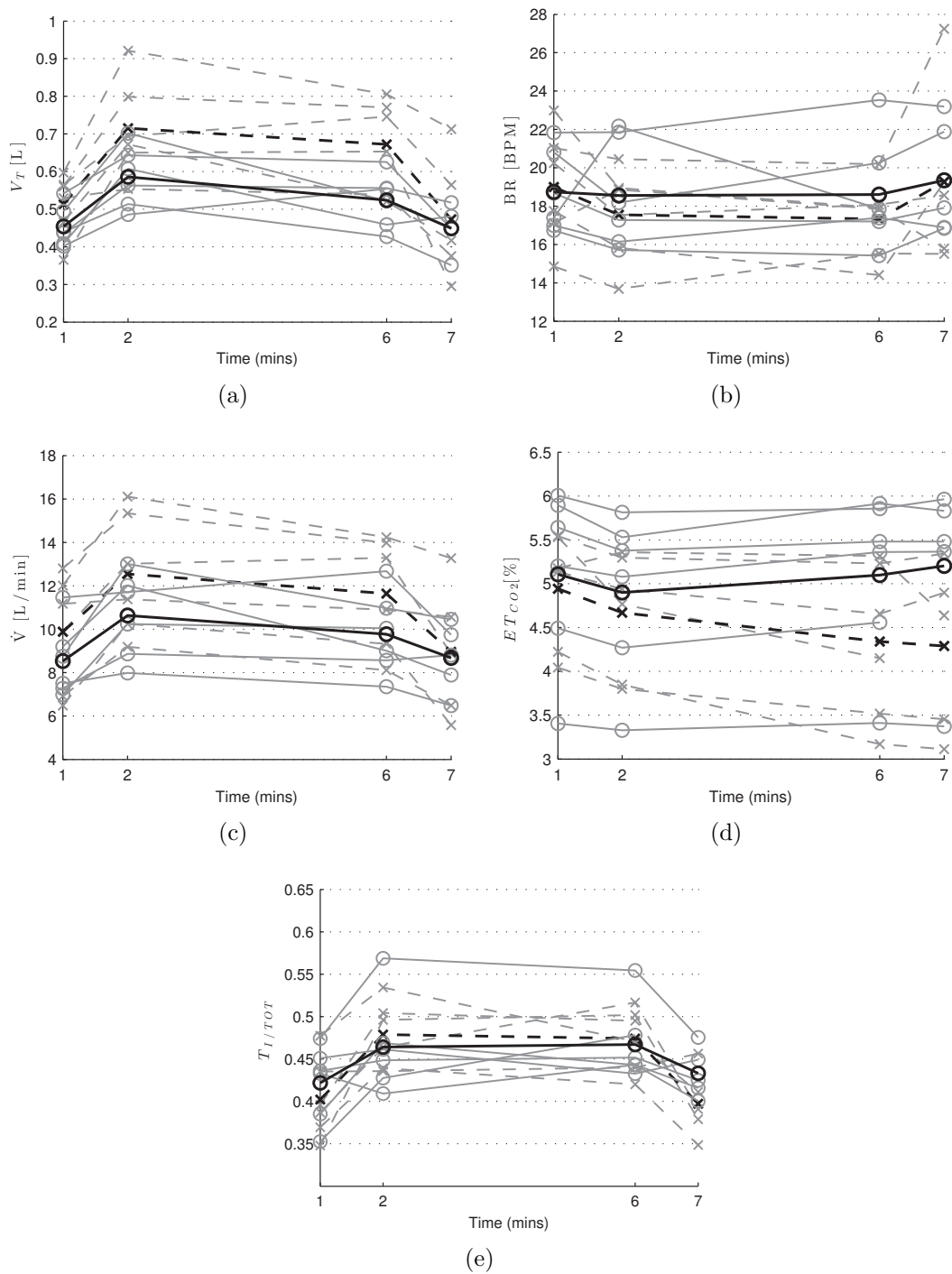
Figure 6.3: Results of the two groups of subjects identified from the response profiles of V_T and ET_{CO_2}. The solid lines represent Group A subjects, the dashed lines represent Group B subjects, the light grey lines represent individual subjects and the black lines represent group means.

Table 6.1: Demographics of the two groups of subjects. Where applicable results are given as mean ± standard deviation. * High injury level was defined as a neurological injury level of C4 or above, low injury level was defined as neurological injury level below C4.

	Group A	Group B
Subjects	S5, S7, S12, S14, S15, S16	S3, S4, S6, S9, S10, S11, S13
N	5	5
Sex (M/F)	5/1	5/1
Age (yrs)	41.2 ± 20.2	37.2 ± 20.4
Height (cm)	177 ± 7.7	176.7 ± 6.2
Weight (kg)	77.2 ± 8.3	70 ± 12.6
Injury level (high/low) *	2/4	2/4
ASIA (A/C)	4/2	4/2
Time post Injury (months)	24.8 ± 36.2	7.8 ± 9.4
Smoker / non-smoker	4/1	4/1

6.3.2 Effect of Abdominal Muscle Training

Figure 6.4 shows the group mean unassisted-QB, AFES-start, AFES-end, and post-AFES outcome measures at each assessment session.

Unassisted-QB

The unassisted-QB results are shown by the crossed marked line in Figure 6.4. V_T, and $T_{I/TOT}$ tended to increase and BR tended to decrease throughout the study. There did not appear to be a change in either $\dot{V}$ or ET_{co_2}. The statistical analysis in Table 6.2 shows that unassisted-QB $T_{I/TOT}$ changed significantly over the study. Post-hoc multiple comparison testing found that A2 was significantly different to A5.

Table 6.2: Overall group mean unassisted ventilatory parameters at each assessment session. F and P are outcomes of the one-way repeated measures ANOVA performed on the data.

	A1	A2	A3	A4	A5	A6	F	*P*
V_T (L)	0.50 (0.10)	0.50 (0.10)	0.55 (0.12)	0.52 (0.16)	0.59 (0.20)	0.52 (0.14)	1.6	0.17
$\dot{V}$ (L/min)	9.60 (2.40)	9.10 (2.30)	11.00 (4.10)	9.00 (3.00)	9.80 (3.40)	9.40 (3.10)	1.1	0.39
BR (BPM)	19.00 (4.10)	18.00 (2.80)	19.00 (3.30)	18.00 (3.30)	17.00 (4.20)	18.00 (4.00)	1.1	0.39
ET_{co_2} (%)	4.90 (0.52)	5.00 (0.62)	5.00 (0.46)	5.10 (0.58)	5.00 (0.41)	5.10 (0.57)	0.7	0.62
$T_{I/TOT}$ ()	0.39 (0.06)	0.40 (0.06)	0.40 (0.07)	0.41 (0.06)	0.42 (0.06)	0.42 (0.06)	2.6	0.03
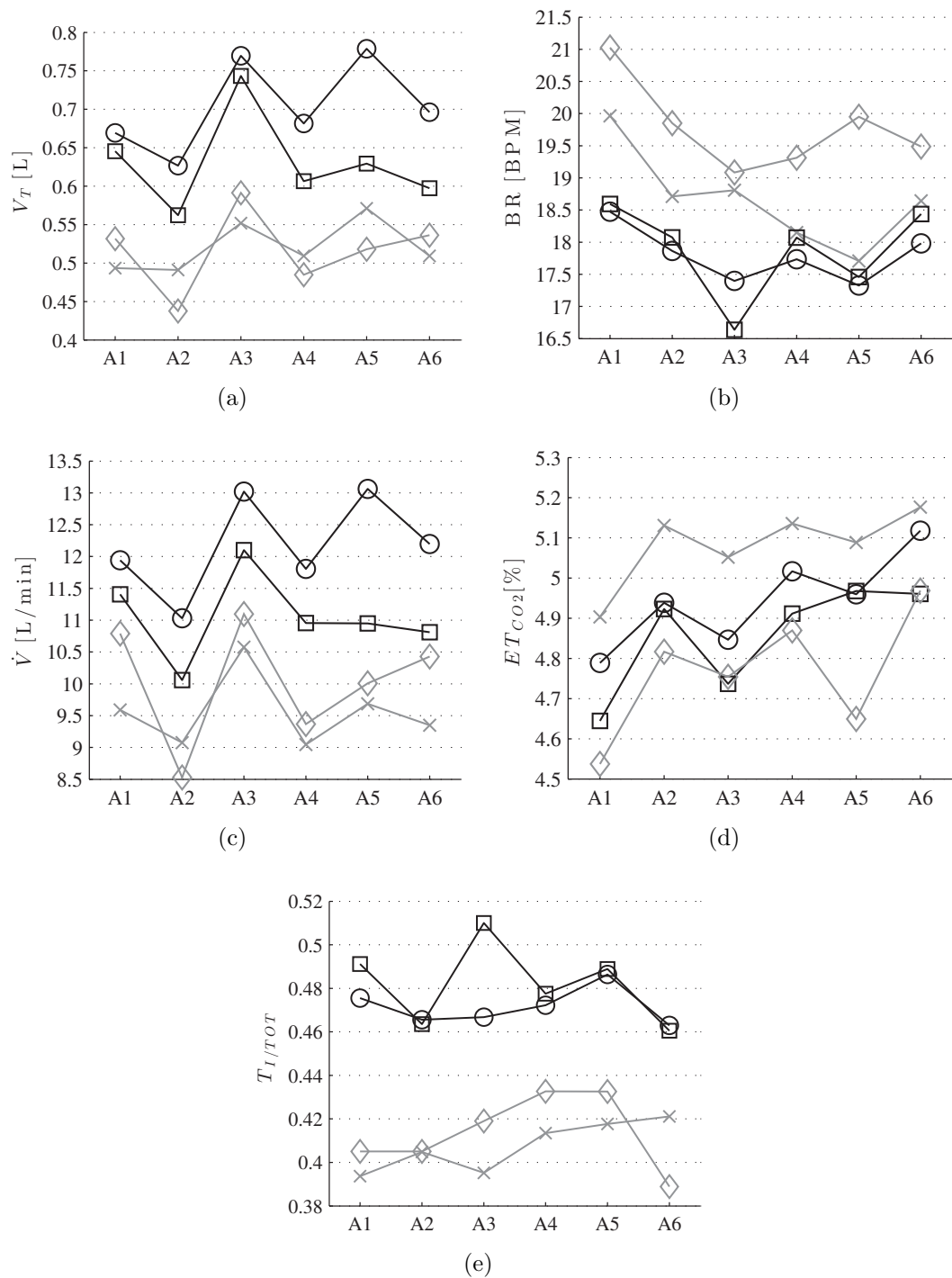
Figure 6.4: The change in the quiet breathing regions throughout the study. The grey lines represent the unassisted regions and the black lines represent the AFES regions. The cross marked line represents unassisted-QB, the circle marked line represents AFES-start, the square marked line represents AFES-end and the diamond marked line represents post-AFES

AFES-Assisted QB

The AFES-assisted quiet breathing regions are shown by the black lines in Figure 6.4. Throughout the study the trends between the quiet breathing regions that were identified in the baseline analysis were consistent.

The difference between unassisted-QB and AFES-start (the cross marked line and the circle marked line, respectively) did not change noticeably throughout the study. The statistical analysis, shown in Table 6.3, found that this difference did not vary significantly for any of the outcome measures.

Table 6.3: The group mean difference between unassisted and the start of AFES-assisted quiet breathing over the course of the study. F and p are outcomes of the one-way repeated measures ANOVA performed on the data.

	A1	A2	A3	A4	A5	A6	F	P
ΔV_T (L)	0.19 (0.22)	0.12 (0.13)	0.19 (0.27)	0.16 (0.20)	0.19 (0.23)	0.16 (0.19)	1.1	0.37
$\Delta \dot{V}$ (L/min)	2.50 (4.00)	1.70 (1.90)	2.30 (2.80)	2.60 (3.10)	3.30 (3.90)	2.50 (3.20)	1.0	0.41
ΔBR (BPM)	-1.50 (3.00)	-0.90 (2.50)	-1.00 (3.40)	-0.35 (1.50)	-0.65 (1.80)	-0.87 (1.90)	0.5	0.75
ΔET_{co2} (%)	-0.19 (0.36)	-0.19 (0.29)	-0.23 (0.26)	-0.11 (0.26)	-0.14 (0.32)	-0.08 (0.32)	1.3	0.29
$\Delta T_{I/TOT}$ ()	0.10 (0.07)	0.07 (0.05)	0.06 (0.04)	0.06 (0.05)	0.08 (0.06)	0.05 (0.06)	1.4	0.24

The difference between the AFES-start and AFES-end (the circle and square marked lines respectively) appeared to increase toward the end of the study for V_T and $\dot{V}$ but not for any of the other outcome measures. Statistical analysis, shown in Table 6.4, found that this difference did not vary significantly for any of the outcome measures.

Table 6.4: The group mean difference between the start and end of AFES -assisted quiet breathing over the course of the study. F and p are outcomes of the one-way repeated measures ANOVA performed on the data.

	A1	A2	A3	A4	A5	A6	F	P
ΔV_T (L)	-0.02 (0.12)	-0.05 (0.08)	-0.01 (0.14)	-0.05 (0.16)	-0.15 (0.24)	-0.09 (0.07)	1.7	0.16
$\Delta \dot{V}$ (L/min)	-0.31 (1.90)	-0.85 (1.30)	-0.69 (2.30)	-0.50 (2.60)	-2.30 (3.60)	-1.50 (1.60)	0.9	0.50
ΔBR (BPM)	0.18 (1.10)	-0.10 (2.20)	-0.65 (2.20)	0.40 (0.77)	0.05 (1.10)	0.30 (1.70)	1.0	0.41
ΔET_{co2} (%)	-0.18 (0.32)	-0.05 (0.46)	-0.13 (0.34)	-0.14 (0.23)	0.02 (0.48)	-0.11 (0.20)	0.6	0.69
$\Delta T_{I/TOT}$ ()	0.01 (0.07)	0.01 (0.03)	0.05 (0.05)	0.00 (0.02)	-0.00 (0.04)	0.00 (0.04)	2.3	0.06

6.4 Discussion

The aims of this study were to characterise the temporal response of the respiratory system to periods of AFES-assisted breathing and to test the hypothesis that a period of abdominal muscle training would improve AFES-assisted and unassisted breathing parameters. The results of this study found that V_T, $\dot{V}$,

$T_{I/TOT}$ were increased and that BR and ET_{CO_2} were reduced during AFES-assisted breathing compared with unassisted breathing. The training programme had a minimal effect on unassisted-QB and no effect on AFES-assisted breathing.

6.4.1 Baseline Response of the Respiratory System to AFES-Assisted Breathing

The results of this study found that there was a significant increase in V_T, $\dot{V}$, and $T_{I/TOT}$, and a tendency for BR and ET_{CO_2} to decrease, during the transition from unassisted breathing to AFES-assisted breathing. During the subsequent five minutes of AFES-assisted breathing V_T, $\dot{V}$, and $T_{I/TOT}$ tended to decrease, BR tended to increase, and ET_{CO_2} remained approximately constant, although these changes were not significant. During the transition from AFES-assisted breathing back to unassisted breathing V_T, $\dot{V}$, $T_{I/TOT}$ and BR returned to their baseline levels, while ET_{CO_2} was reduced slightly compared with its baseline level.

Tidal Volume

The change in V_T during the initial AFES response corroborates the results reported by other authors [57–59, 78, 132, 134]. When the abdominal muscles contract during exhalation, the abdominal contents are pushed upward toward the bottom of the lung. This movement causes the lung to empty past FRC and augments expiratory volume. The subsequent inhalation is augmented as a result of the passive recoil of the lung from FRC.

Throughout the five minute period of AFES-assisted breathing the stimulation pulse width was adjusted to maintain a constant visual contraction of the abdominal muscles, in order to minmise the effect of abdominal muscle fatigue on AFES-assisted breathing. Although V_T tended to decrease slightly during this period, the lack of significant change suggests that this strategy was effective. A limitation of using V_T to assess muscle fatigue (or lack thereof) instead of a more direct measure of abdominal muscle contraction, such as gastric pressure, is that V_T is also affected by the work done by the inspiratory muscles.

Breathing Rate

Although BR did not change significantly during the initial AFES response, it decreased for the majority of subjects. In addition, there was a significant increase in $T_{I/TOT}$ during the initial AFES response. These results indicate that

AFES influenced the breathing pattern of subjects. Since the timing of stimulation was paced by the subjects' volitional breathing pattern, AFES must have affected BR and $T_{I/TOT}$ indirectly. A possible explanation is that the cessation of stimulation during expiration, resulted in an acute reduction in gastric, and in turn intrathoracic, pressure that prematurely initiated inhalation. This reasoning is supported by the increase in $T_{I/TOT}$, which shows that expiratory time was reduced in relation to inspiratory time, between unassisted and AFES-assisted breathing. Previous studies have reported mixed effects of AFES-assisted breathing on subjects' breathing rate. While the tendency for BR to decrease was observed by Gollee et al. [57–59], an increase in BR has been observed by others [132, 134]. Since this study and all previous research has used a one second stimulation burst during exhalation, the reason for the difference in reports of the effect of AFES on BR is unclear.

Minute Ventilation

The trend in $\dot{V}$ generally followed the trend in V_T throughout the testing protocol. This shows that the reduction in BR was more than offset by the corresponding increase in V_T. An important aspect of ventilation is the ratio of dead space ventilation to total ventilation (i.e. the ratio of the air that is inhaled and not being used to oxygenate the blood). Although this ratio was not measured in this study, the pattern of increased $\dot{V}$ through an increased V_T and reduced BR suggests that alveolar ventilation was increased [79]. The increase in unassisted $\dot{V}$ as a result of AFES-assisted breathing has been reported by previous authors [57–59, 132, 134].

End Tidal Carbon Dioxide

While the change in ET_{CO_2} during the quiet breathing test for the overall group was not significant, ET_{CO_2} decreased between unassisted breathing and the onset of AFES-assisted breathing in eleven out of the thirteen subjects who responded to AFES-assisted breathing. ET_{CO_2} continued to decrease throughout the five minute period of AFES-assisted breathing for six of the responder subjects (Group A) and returned to its baseline level for the other six responder subjects (Group B). The only difference between the two groups was that the Group A subjects had a significantly greater increase in V_T during the initial AFES response.

ET_{CO_2} is a surrogate measure for arterial partial pressure of carbon dioxide, which is a primary mediator in the neural control of respiration [150]. An increase in the arterial partial pressure of carbon dioxide stimulates chemoreceptors in the

medulla and peripheral nervous system which in turn increase $\dot{V}$ so that the excess carbon dioxide is removed from the body.

A reduction in arterial partial pressure of carbon dioxide may be caused by an increased $\dot{V}$, a reduced metabolic rate, an acute decrease in body temperature, and reduced cardiac output [149]. AFES-assisted breathing has been used previously to increase cardiac output [140], it should increase metabolic rate through the contraction of the abdominal muscles, and is unlikely to have an effect on body temperature. These three factors would all increase arterial partial pressure of carbon dioxide during AFES-assisted breathing.

In the Group A subjects, ET_{CO_2} decreased during the transition from unassisted to AFES-assisted breathing, and decreased further over the five minutes of AFES-assisted breathing. This trend suggests that in these patients the increase in $\dot{V}$ during AFES-assisted breathing more than offset the increase in metabolic and cardiac output caused by AFES.

In the Group B subjects, ET_{CO_2} decreased during the transition from unassisted to AFES-assisted breathing, and increased back to baseline levels over the five minutes of AFES-assisted breathing. These results suggest that the initial increase in ET_{CO_2} was transient and caused by the step change in $\dot{V}$ and that ET_{CO_2} at the end of the five minutes reflected the steady-state ET_{CO_2} during AFES-assisted breathing [139]. The fact that ET_{CO_2} at the end of five minutes of AFES-assisted breathing was similar to the ET_{CO_2} during baseline unassisted breathing suggests that the increase in $\dot{V}$ during AFES-assisted breathing offset the increase in metabolic and cardiac output caused by AFES.

For the non-responder subjects, whose AFES-assisted V_T was not greater than their unassisted V_T, and the responder subject who had the smallest difference between unassisted and AFES-assisted V_T, the increase in ET_{CO_2} during AFES-assisted breathing suggests that AFES-assisted breathing increased the arterial partial pressure of carbon dioxide.

These results have clinical implications. Excess carbon dioxide in the blood (hypercapnia) can cause dyspnea in mild cases to unconsciousness in severe cases. Low levels of carbon dioxide in the blood (hypocapnia) can cause light headedness and dizziness. To avoid these situations the results of this study suggest that AFES should not be used with the non-responder group of subjects and that the effect of AFES should be reduced (possibly by reducing the stimulation intensity or by reducing the number of breaths that are stimulated) in the Group A subjects.

6.4.2 Effect of Training on the Respiratory Response to AFES-Assisted Breathing

This is the first study that has investigated the effect of abdominal muscle training on AFES-assisted breathing. The results of this study did not find a statistically significant change in either the difference between unassisted breathing and the onset of AFES-assisted breathing, or the difference between the start and end of five minutes of AFES-assisted breathing. While in some individual subjects there appeared to be a training effect there were no consistent patterns of change observed in sub-groups of subjects.

The results of this study are contrary to the original hypothesis which was that training would increase the power, and in turn the effect of AFES on V_T, by reversing the atrophy of the abdominal muscles caused by SCI. There are at least two possible explanations for the negative result of this study:

1. The duration of the training programme was not sufficient (discussed in Chapter 4)

2. The design of the training programme was not suitable to induce changes in abdominal muscle strength (discussed in Chapter 4)

It is possible that the training programme affected the fatigue resistance of the abdominal muscles. However, the experiments of this study did not include a measurement of abdominal muscle fatigue. Future work should investigate this aspect of abdominal muscle training, as the endurance time of the abdominal muscles is an important aspect of AFES-assisted breathing.

The Effect of Training on Unassisted Quiet Breathing

The results of this study showed that $T_{I/TOT}$ increased significantly and V_T tended to increase over the training period. The tendency for V_T to increase over the training period may be explained by the corresponding increase in FVC that was found in Chapter 4, as well as by previous authors investigating AFES based respiratory muscle training programmes [27,159]. Switching to a pattern of slower, deeper breathing would reduce dead space ventilation and thus improve the efficiency of breathing, which in turn is likely to improve patient comfort and potentially aid in reducing respiratory complications. The reasons for the lack of significant change in V_T, BR or $\dot{V}$ were covered in the discussion of the effect of training on AFES-assisted breathing. One additional reason, is that the overall group mean quiet breathing V_T, BR and $\dot{V}$ of the subject group studied were

within the normal range and therefore there was no physiological basis to support a change in breathing pattern.

6.5   Study limitations

There were at least two limitations of the experiments described in this chapter:

1. The changes in ET_{CO_2} may not accurately reflect the changes in the arterial partial pressure of carbon dioxide. The correlation of these variables is affected by changes in the dead space to V_T ratio [110], which can be altered by changes in breathing pattern [79]. The positive gradient between the arterial partial pressure of carbon dioxide and ET_{CO_2} reduces with progressive reductions in the dead space to V_T ratio; with all other factors remaining constant a reduction in the dead space to V_T ratio would result in an increased ET_{CO_2} for a given arterial partial pressure of carbon dioxide. Given that AFES-assisted breathing results in an increased V_T and reduced BR, it should also have a reduced dead-space to V_T ratio [79]. Therefore, the author believes that the use of ET_{CO_2} as a surrogate measure may have underestimated the changes in arterial partial pressure of carbon dioxide that occurred during AFES-assisted breathing.

2. The length of the AFES-assisted breathing section of the test was short. While the results of this study showed that AFES-assisted breathing could augment ventilation for short periods of time, future work needs to determine the limit of AFES-assisted breathing as a tool to augment ventilation in tetraplegia.

6.6   Conclusions

1. AFES-assisted breathing results in increased V_T, $\dot{V}$, and $T_{I/TOT}$, and reduced BR compared with unassisted breathing.

2. In patients whose AFES-assisted V_T is greater than their unassisted V_T, the increased $\dot{V}$ during AFES-assisted breathing offsets any increase in metabolic or cardiac output that would be expected during AFES-assisted breathing.

3. Three weeks of abdominal muscle training does not affect AFES-assisted ventilatory parameters and but may have a minimal effect of unassisted ventilatory parameters.

Chapter 7

Ventilator Weaning with AFES

7.1 Introduction

MV is commonly required during the initial stages of injury for individuals with a cervical SCI [32, 152]. For motor complete injuries above C3, MV is required because the diaphragm and other breathing muscles are completely paralysed [32, 152]. For individuals who maintain partial or complete diaphragm function, there are several reasons why MV might be required. Firstly, there may be bleeding or swelling at the level of trauma that can cause the neurological level of the injury to rise by up to two levels [152]. Secondly, there is increased load on the diaphragm as a result of paralysis of the other respiratory muscles and/or respiratory infection which can cause diaphragmatic fatigue [127, 152]. Incidence of tetraplegic individuals requiring ventilation varies between reports. In one study incidence was reported at 90% [32] whereas in another study, incidence of ventilatory failure in cervical SCI individuals was 29% [74]. Both of these reports found that the incidence of MV is greater in those with the highest levels of injury.

It may be possible to wean those tetraplegic individuals whose diaphragm is not completely paralysed from MV. The likelihood of weaning and length of time taken to wean depends on several factors: the neurological level of injury, the age of the individual, co-morbidities and the development of respiratory infection during the weaning process [152]. Weaning success and duration may also be affected by non-patient related factors such as the type of weaning method used (e.g. progressive ventilator free breathing weaning vs. intermittant mandatory ventilation) [21, 47, 119], ventilator volume settings [120], and the initiation of the weaning process by the individual's physician [19]. Weaning an individual from MV is of paramount importance as prolonged MV can increase the risk of respiratory infection (for example, ventilator induced pneumonia) [19] and

cause respiratory muscle weakness [143]. Furthermore, ventilator dependency in individuals is associated with lower survival rates than individuals who are weaned from MV [152].

Although weaning techniques differ in their implementation, the general goal is to reduce progressively the work of breathing accomplished by the ventilator and thus recondition the respiratory muscles that have been weakened during the period of MV [47]. It follows that interventions that allow this process to begin earlier and target the strength of the respiratory muscles may assist with weaning in these individuals. It has been shown that:

- AFES can be used to improve V_T in spontaneously breathing tetraplegic individuals (Chapter 6), [58, 132, 134].

- AFES can be used to support short periods of ventilator free breathing in tetraplegic individuals who are otherwise ventilator dependent [78].

- AFES based training paradigms can improve unassisted respiratory function (Chapter 4), [27, 87, 159]

Consequently, it was hypothesised that incorporating AFES into the weaning process would allow weaning both to begin earlier and reduce the time to wean. The aim of this study was to demonstrate the feasibility of this approach by combining AFES with a standard weaning protocol for a single tetraplegic patient.

7.2 Materials and Methods

7.2.1 Case Study

This study included a twenty-four year old man with a C4/C5 spinal fracture dislocation and head injury. Upon entry to the spinal unit the neurological injury was classified at level C2 and severity AIS A. Five months after injury, the patient's neurological injury was reclassified at level C4/C5 and severity AIS A.

At the start of this study the patient had been injured for two months and was able to sustain volitional ventilation for up to three minutes. He had a tracheostomy and was completely reliant on MV.

7.2.2 Study Outline

This study lasted for a total duration of twenty-eight weeks and included two phases which were timed as shown in Figure 7.1(a). AFES was used to complement standard of care which included a progressive ventilator free breathing weaning programme. During progressive ventilator free breathing weaning, the patient is required to breathe without ventilator support during daily trials (known as Spontaneous Breathing Trials (SBTs)) which progressively increase in duration until the patient is completely weaned from MV.

Both phases of the study included AFES SBTs described in Section 7.2.4 and respiratory assessment sessions described in Section 7.2.5. An outline of the timeline of the AFES SBTs and assessment sessions is given in Figure 7.1(b) for phase 1 and in Figure 7.1(c) for phase 2.

7.2.3 AFES

AFES was applied over the rectus abdominis and external oblique muscle groups using a constant stimulation frequency of 30 Hz. During the training and assessment sessions current was kept constant while pulse width was increased to account for muscle fatigue. During the AFES SBTs and the assessment sessions which used the stimulators on-board program, the stimulation pulse width had a ramp up time of 0.1 s and a 0 s ramp down time. During the assessment sessions which used the automatic stimulation system, the stimulation pulse width was filtered using a 2nd order transfer function with a 0.1 s rise time. Stimulation set up followed the same methodology that was used in the study of spontaneously breathing tetraplegics (Chapter 3). The stimulation settings used in this study were chosen based on the settings used in the previous study.

7.2.4 AFES Spontaneous Breathing Trials

AFES-SBTs were prescribed up to five times per week for the durations given in Figures 7.1(b) and 7.1(c). During the AFES-SBTs the on-board programme on the stimulator was used as described in Chapter 3. The programme cycle period and stimulation on-time were set to match the breathing period and expiratory time normally provided by the ventilator. Stimulation was turned on before the patient was disconnected from MV. When the patient was comfortable, MV was removed and the patient was cued to breathe in time with the stimulation. During the training sessions up to A1 the cue was given verbally using the instructions 'breathe in, breathe out'. In all training sessions subsequent to A1, a balloon was

(a) Overview of the study protocol
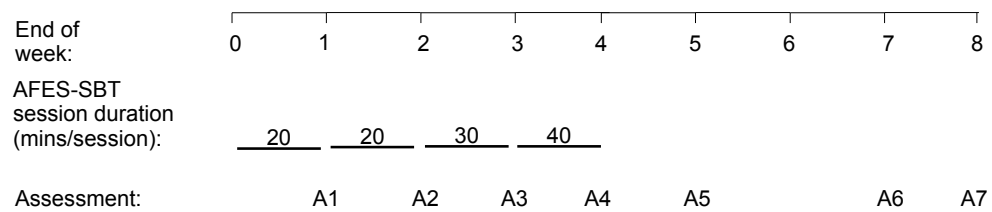
(b) Outline of phase 1
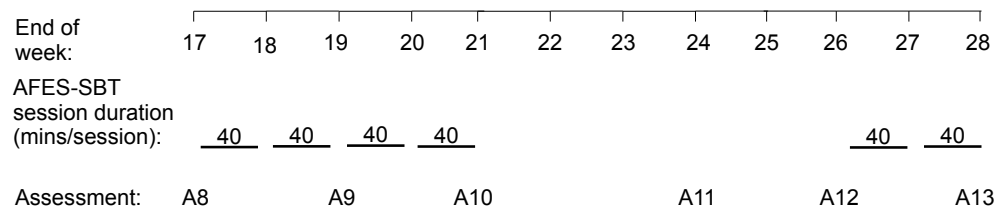
(c) Outline of phase 2

Figure 7.1: Study protocol. AFES SBTs were completed up to five time per week.

attached to the mechanical ventilator and the patient was coached to inhale and exhale in time with the balloon's inflation and deflation. Throughout the training sessions, the patient's blood oxygen saturation was monitored and recorded, by hand, every minute. If the patient's blood oxygen saturation level dropped below 92% during the training session, MV was immediately re-instituted. The patient remained on MV in combination with AFES, until the patient's consultant felt comfortable removing MV again. This process of AFES-assisted breathing with and without MV continued for the duration of the session.

7.2.5 Assessment Sessions

As shown in Figures 7.1(b) and 7.1(c), the whole study consisted of a total of thirteen assessment sessions. Each assessment session included a series of respiratory tests as illustrated in Figure 7.2.

The tests of unassisted breathing, AFES-only breathing and AFES-assisted breathing, lasted for 2 minutes or until the patient's blood oxygen saturation level dropped below 92%. The test of max unassisted and max AFES-assisted breathing lasted for one minute. A description of each of the breathing tests is given below:

Unassisted breathing The patient was asked to breathe without the assistance of MV or AFES.

AFES-only breathing The patient was asked to relax and to attempt to let AFES support breathing completely.

AFES-assisted breathing The patient was asked to breathe normally while being assisted with AFES.

Max unassisted breathing The patient was asked to breathe with maximum effort without the assistance of MV or AFES

Max AFES-assisted breathing The patient was asked to breathe with maximum effort while being assisted with AFES.
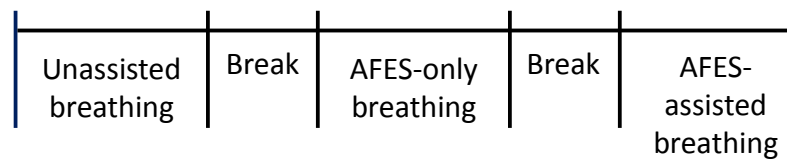
(a) Outline of the tests conducted in assessments A1 to A5
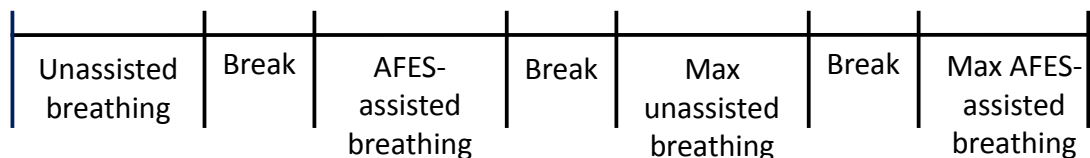
(b) Outline of the tests conducted in assessments A6 to A13

Figure 7.2: An outline of the tests conducted in each of the assessment sessions

Maximum unassisted and AFES-assisted breathing were not specifically tested in assessment sessions A1 to A5 since the patient had to use maximum effort during the unassisted and AFES-assisted breathing tests to sustain MV free breathing. The AFES-only breathing test was included in assessment sessions A1 to A5 only. After this point the patient could maintain spontaneous ventilation without conscious effort.

During the assessment sessions, the patient's ventilation was measured using the spirometer in 'live mode', as described in Chapter 3. In assessment sessions A1 to A5 the spirometer was connected to the patient's tracheostomy whereas in assessment sessions A6 to A13 the spirometer was connected to a full face mask. The stimulator's on-board programme was used in assessment sessions A1 to A6. The programme cycle period and stimulation on-time were set to match the breathing period and expiratory time normally provided by the ventilator. Stimulation was synchronised with the patient's volitional breathing using the balloon method described Section 7.2.4. In A1 and A2 the cycle period was set equivalent to 13 breaths/min with a stimulation on-time of 40%. In A2 to A5 the cycle period was set equivalent to 13 breaths/min with a stimulation on-time of 50%. In A6 the cycle period was set equivalent to 30 breaths/min with a stimulation on-time of 50%. In assessment sessions A7 to A13 stimulation was synchronised with the patient's volitional exhalation using the quiet breathing trigger described in Chapter 3

7.2.6 Additional Measurements

The patient's diaphragm movement was assessed by fluoroscopy one week prior to the start of study and at the beginning of week seventeen (one week prior to A8). Diaphragm movement was assessed while the patient was supine under two conditions: unassisted and AFES-assisted breathing. Under both of these conditions the patient was asked to breathe with maximum effort. During AFES-assisted breathing, the stimulation intensity was set to give a strong even contraction of the abdominal muscles (Section 3.2.1 on page 53). Triggering of the stimulation was accomplished by manually timing stimulation to coincide with the complete voluntary expiratory phase of the patient's breathing.

The nurses medical notes were available for this study. From these notes the duration of the patients regular unassisted SBTs were recorded.

7.2.7   Analysis

Using the recorded output of the spirometer, V_T, $\dot{V}$ and BR were calculated using the methods described in Chapter 3. For each assessment session for the unassisted, AFES-only and AFES-assisted breathing tests, the mean was calculated over every breath recorded in each test. For the maximum unassisted and AFES-assisted breathing tests, the mean V_T, $\dot{V}$ and BR were calculated over the three breaths which had the greatest V_T.

From the videos recorded from the fluoroscopy sessions each frame was visually inspected and the frames which corresponded to the beginning and end of inhalation were extracted. The position of the diaphragm in relation to the ruler that was placed over the abdomen during the recording was noted for each of these images and diaphragm movement was calculated accordingly.

7.3   Results

7.3.1   Diaphragm Fluoroscopy

Figure 7.3 shows still images from the diaphragm fluoroscopy which was completed prior to the start of the study. As can be seen in the figure, during this session, diaphragm movement was less that 1 cm during unassisted breathing (Figures 7.3(a) and 7.3(b)) and approximately 2 cm during AFES-assisted breathing (Figures 7.3(c) and 7.3(d)). In the second fluoroscopic assessment (beginning of study week seventeen), diaphragm movement was approximately 5 cm during unassisted breathing and approximately 8 cm during AFES-assisted breathing.

7.3.2   Spontaneous Breathing Trial Duration

Figure 7.4 shows the duration of the AFES-SBTs and unassisted SBTs during the first phase of the intervention. The figure demonstrates:

1. For the first three weeks of the study the patient was able to sustain much longer periods of ventilator free breathing while assisted with AFES than with volitional breathing.

2. AFES weaning sessions started approximately three weeks sooner than the unassisted weaning sessions. However once unassisted SBTs were started, the patient made rapid progress.

Figure 7.5 shows the duration of unassisted SBTs from the start to the end of the study. Following the first phase of the intervention, unassisted SBT duration
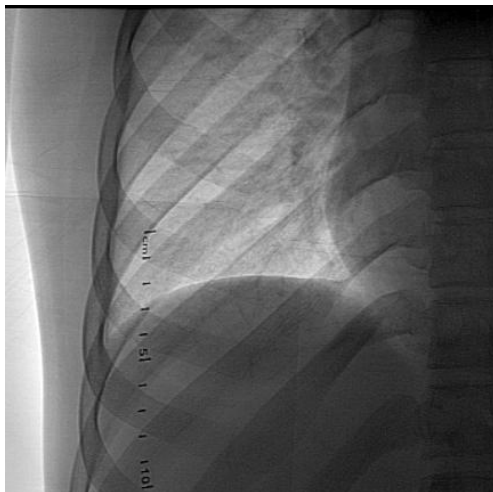
(a) Diaphragm position at the end of unassisted inhalation
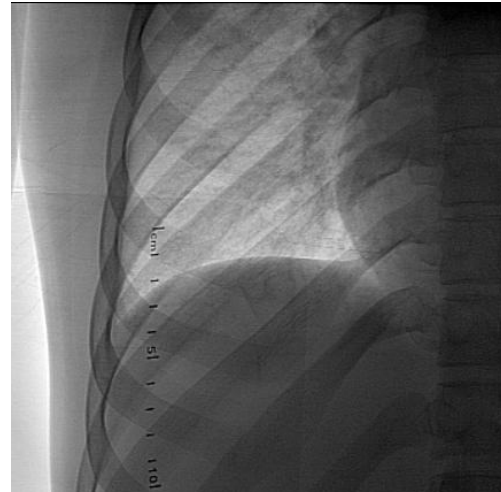
(b) Diaphragm position at the end of unassisted exhalation
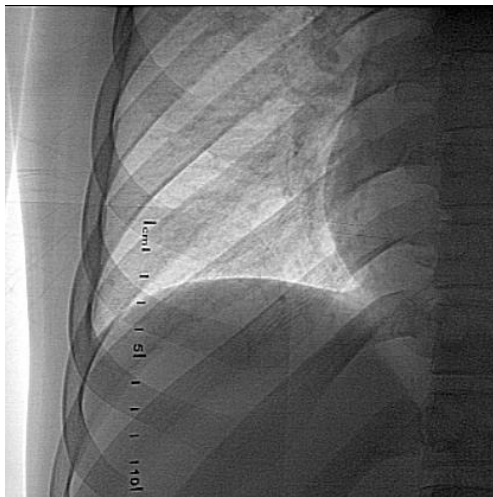
(c) Diaphragm position at the end of AFES-assisted inhalation
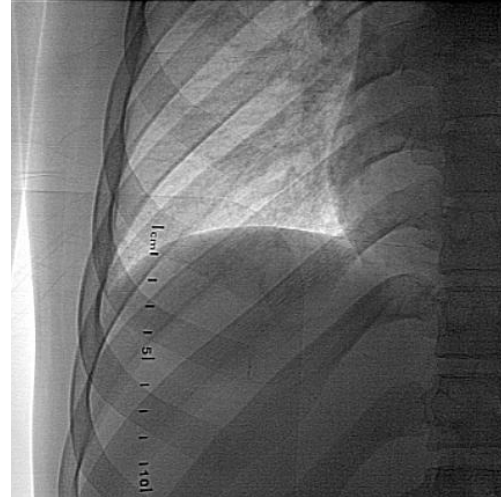
(d) Diaphragm position at the end of AFES-assisted exhalation

Figure 7.3: Diaphragm fluoroscopy during unassisted and AFES-assisted breathing before the start of the study. The scale shown in the pictures is in increments of 1 cm. Diaphragm movement during unassisted breathing was less than 1 cm. Diaphragm movement during AFES-assisted breathing was approximately 2 cm

increased rapidly until week nine at which point progress almost stalled at 12 hours/day. By the start of week fifteen, the duration of the unassisted SBTs had only increased to thirteen hours/day. Furthermore the patient's nurses had attempted longer daily times but had noted that the patient's blood gas levels had become unstable. During week fifteen, the patient's condition became worse and he was only able to sustain 10 hours/day of ventilator free breathing. The second phase of the study started at the beginning of week seventeen. From this point the patient made steady progress until the start of week twenty six when
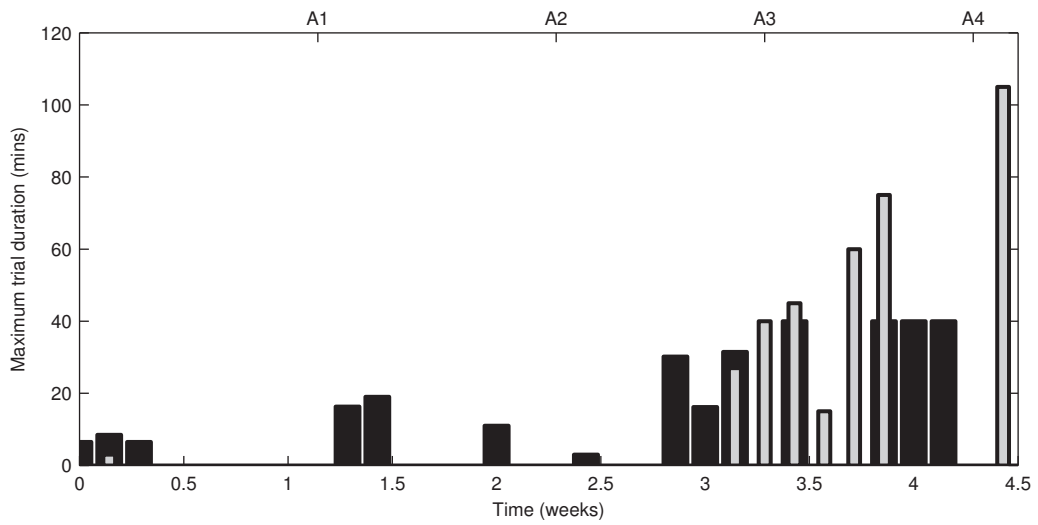
Figure 7.4: Maximum AFES-SBT (shown as the black bars) and unassisted SBT (shown as the grey bars) duration through the initial weeks of the study.

the patient was completely weaned from MV.
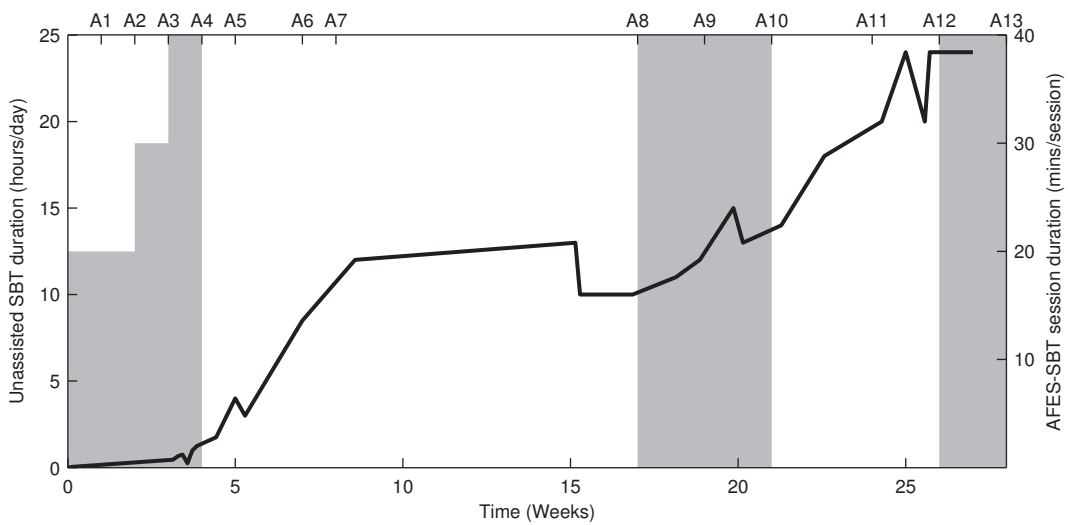
Figure 7.5: Change in unassisted SBT duration (shown by the black line and the left y-axis) compared with the timing and duration of AFES-SBT sessions (shown by the shaded grey areas and the right y-axis) throughout the study.

7.3.3 Respiratory Measurements

Figures 7.6(a), 7.6(b) and 7.6(c) on page 143 show the change in V_T, $\dot{V}$ and BR throughout the study for the different breathing tests conducted in each assessment session. During assessment session A5 the patient was feeling generally below par. A6 was the first assessment in which ventilation was measured using the face mask as opposed to the tracheostomy. A6 was also the first assessment

in which a distinction was made between quiet breathing and breathing with maximum effort.

7.4 Discussion

The major finding of this study is that it is feasible to incorporate AFES into the weaning process of a tetraplegic subject. This study also provided preliminary data to support the hypothesis that using AFES to assist weaning a patient off MV would allow the weaning process to begin earlier than otherwise possible and may reduce the time to wean by improving unassisted ventilatory parameters.

7.4.1 Initial Spontaneous Breathing Trials

At the start of the study, AFES-SBTs could last considerably longer than unassisted SBTs (10 minutes compared with 3 minutes, Figure 7.4). Since the patient was able to tolerate longer AFES-SBTs than unassisted SBTs, the patient was willing to participate in AFES-SBTs approximately three weeks before regular unassisted SBTs started. Once regular unassisted SBTs begun, progress was rapid, increasing from 30 minutes per day to 110 minutes per day over the course of one week. It is clear from the results of this study that, in this case, AFES allowed the weaning process to begin earlier than would have been otherwise possible.

7.4.2 Weaning from Mechanical Ventilation

After the cessation of AFES-SBTs, at the end of week four, unassisted SBT duration continued to progress quickly, reaching 12 hours per day at week nine of the study. In the subsequent six weeks the patient made only a modest gain in unassisted SBT duration and during week fifteen, unassisted SBT duration declined. Therefore, in week seventeen, another period of AFES-SBTs was initiated. Through the following four weeks of AFES-SBTs the patient's unassisted SBT duration started increasing again. Unassisted SBT duration continued to increase after the conclusion of the second period of AFES-SBTs until, during week twenty six, the patient was completely weaned from MV.

Firm conclusions cannot be drawn from the trend described above because this is a single case study. However, the increase in unassisted SBT duration over the whole study, and, in particular, the increase in unassisted SBT duration during the second period of AFES-SBTs, following the stall in progress during
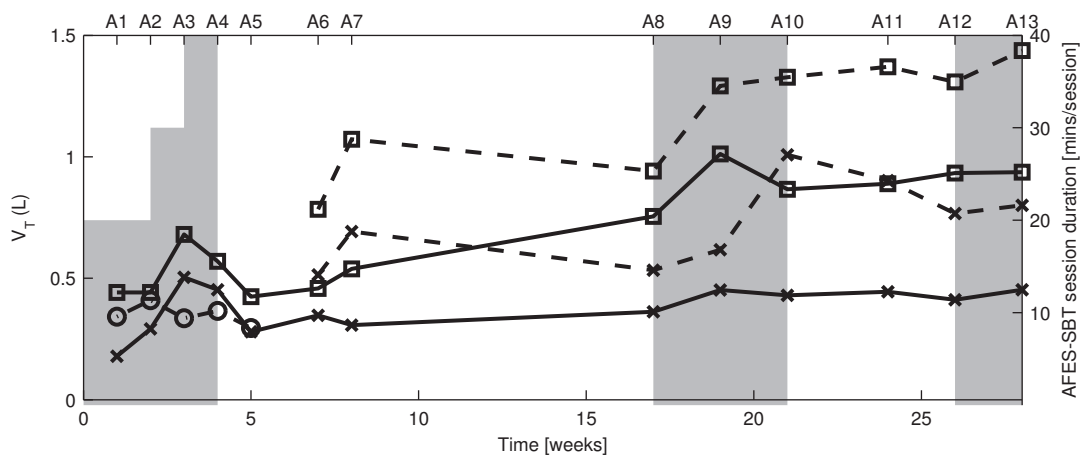
(a) Tidal volume
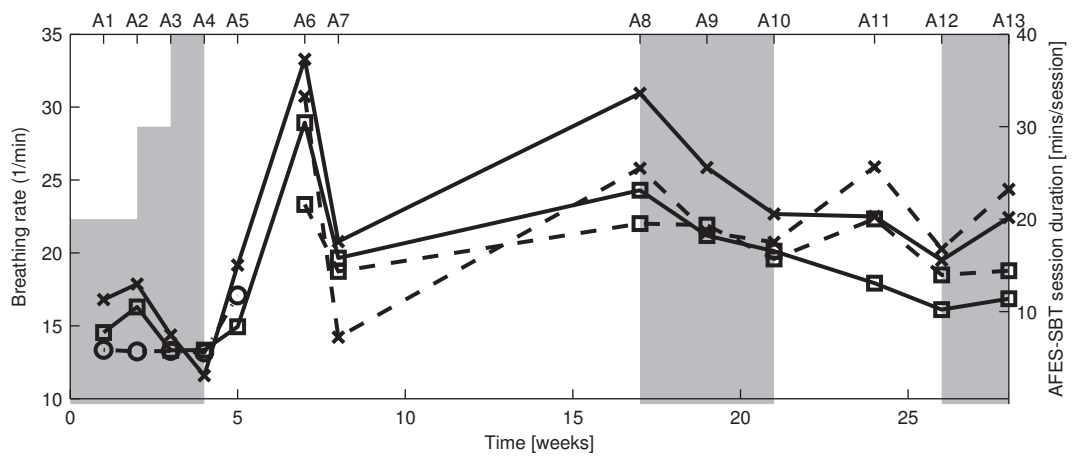
(b) Breathing rate
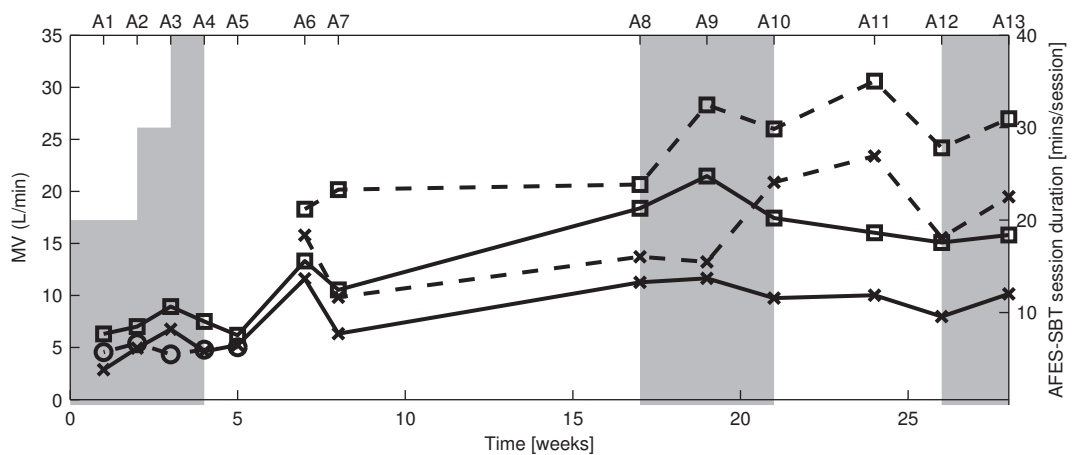
(c) Minute Ventilation

Figure 7.6: Respiratory measurements (shown by the lines and left y-axis) compared with the timing and duration of AFES-SBTs (shown by the shaded grey areas and the right y-axis) throughout the study. Lines with square's as data points indicate AFES-assisted respiratory measures; lines with x's as data points indicate unassisted respiratory measures; lines with circles as data points indicate AFES-only respiratory measures. Solid lines indicate quiet breathing; dashed lines indicate maximum breathing.

the prior 8 weeks, certainly suggests that the intervention had an effect on the weaning outcome of this patient.

7.4.3 Potential Mechanisms

The difference between AFES-SBT and unassisted SBT duration, over the initial four weeks of the study, can be explained by the augmented V_T and $\dot{V}$ during AFES-assisted breathing compared with unassisted breathing. AFES increases V_T by compressing the abdominal contents, which, in turn, push upward on the diaphragm. This mechanism is clearly illustrated by the results of the diaphragm fluoroscopy sessions which showed a substantial difference in vertical diaphragm displacement during AFES-assisted breathing compared with unassisted breathing.

The trend in unassisted SBT duration appeared to be highly correlated with underlying changes in the patient's ventilatory parameters. During phase 1 of the study, in which unassisted SBT duration increased substantially, there was a considerable increase in V_T and $\dot{V}$ (It should be noted that during A1 to A6 the measurements of breathing rate are not representative as the patient was asked to follow a set rate). Between A7 and A8, through which there was a net decline in unassisted SBT, there was a decline in maximum unassisted V_T and a sharp rise in both maximum and quiet unassisted BR. At the start of phase two in the study, unassisted SBT progress resumed, and there was a corresponding increase in maximum unassisted V_T and decrease in both maximum and quiet unassisted BR. The correlation between V_T and duration of U-SBT may lie in the difference between maximum and quiet unassisted V_T. As the difference between quiet V_T and maximum V_T increases, the effort required to expand the lungs decreases, and the respiratory musculature suffers less fatigue. The reduced difference between maximum and quiet V_T between A7 and A8 also explains the increased BR between A7 and A8.

It is possible that the change in ventilatory parameters would have occurred without the intervention of AFES [86] and from the results of a single case study it is not possible to draw conclusions to the contrary. However, it is persuasive that the greatest improvement in ventilatory parameters occurred during the periods of AFES-SBTs. This observation also agrees with the findings in Chapter 4, which showed a statistically significant increase in FVC following three weeks of AFES training, and the findings by other authors that have shown AFES training can improve unassisted FVC [27, 87, 159].

If the AFES-SBT intervention was responsible for the progression in unassisted SBT duration there are several possible explanations:

1. AFES improved the bulk of abdominal muscles which increased inhalation capacity through the fulcrum effect [84, 154] (explained fully in Chapter 4).

2. AFES affected the diaphragm through two complimentary mechanisms:

   (a) in addition to abdominal muscle recruitment, AFES also recruited the diaphragm

   (b) it also moved the diaphragm though a greater range of motion compared with unassisted breathing. This passive diaphragmatic stretch, in turn might have preserved the architecture of muscle fibres in a similar way to the purported effect of passive range of motion exercises applied to locomotor muscles [68].

3. The higher lung volumes associated with AFES-assisted breathing may have recruited additional elements of the lung and helped clear atelectasis. The subsequent increase in compliance would have reduced the work of breathing and aided in the weaning process [120].

4. The co-ordination of the breathing muscles is a complex task requiring input from several pathways, which are disrupted following a tetraplegic SCI [141]. By following a set breathing pattern and, at the same time contracting the abdominal muscles to reduce the load on the other breathing muscles, the patient may have been able to relearn how to co-ordinate his neurologically intact breathing muscles.

7.4.4 Clinical Implications

Weaning from MV has important clinical implications. MV is a life-saving intervention for many SCI patients. However prolonged use of MV is associated with increased respiratory complications, particularly ventilator associated pneumonia. Lifelong use of MV is also associated with a severely reduced five year survival rate when compared with spontaneously breathing tetraplegics [152]. In addition life-long ventilator use is associated with a lower quality of life when compared with ventilator free patients. While there have been other respiratory muscle training programs used to improve weaning outcomes for tetraplegic and non-SCI patients [137], this is the first study demonstrating an AFES-based respiratory muscle training programme for ventilator weaning in tetraplegia.

Of the other approaches, inspiratory muscle training using resistive mouthpiece devices has received the most attention. Inspiratory muscle training has been shown to be effective at improving weaning outcome in non-SCI patients with prolonged MV [100, 101]. There is also evidence that inspiratory muscle training may be useful in spontaneously breathing tetraplegic patients [137, 147]. However inspiratory muscle training has not been tested in ventilator dependent SCI. If a patient fails to wean it may be possible to use an implanted diaphragm pacing system as an alternative to MV [37, 38, 42, 43, 71, 130]. However this approach may not be suitable for every patient and may be associated with complications [71, 130]. Therefore, following validation with future research, the weaning technique demonstrated in this study would provide clinicians with another tool to use before an implant or lifelong ventilation is necessary.

In addition to the clinical benefits weaning from MV has for a patient, improving weaning outcome and reducing time to wean has economic implications. Days spent in an intensive care unit are expensive for the health care provider. Daily costs in the intensive care unit are reported to be around $4000 per day in the United States [157] and 2000 Euros per day in Europe [71]. If the intervention proposed in this case study is shown to be generally successful it has the potential to improve the health of patients and offer a fiscal benefit to the health care provider.

7.4.5 Study Limitations

The major limitation of this study was that it comprised a single case study. In addition there were two other limitations:

1. During the assessments A1 to A6, AFES was set at a constant rate to which the patient was asked to synchronise his breathing. Inevitably this resulted in a discrepancy between the application of stimulation and the patient's exhalation. This can be observed in the BR recorded for unassisted breathing and AFES-assisted breathing during these assessment sessions. BR should have been at 13 breaths per minute in these assessments (30 breaths per minute in A6) however as can be seen in Figure 7.6(b), it was often much higher than this.

2. During phase two of the study, the assessment sessions generally took place during unassisted SBT. Although the assessments were carried out at the same time of day, they did not necessarily take place at a constant time

in relation to the start of unassisted SBT. As a result patient fatigue may
have unevenly affected the results of these assessments.

7.5 Conclusions

The results of this study demonstrate the feasibility of using AFES in the process
of weaning a tetraplegic patient off MV. AFES can be used to allow the wean-
ing process to begin earlier than standard progressive ventilator free breathing
weaning and increase the duration of unassisted SBTs at the start of the weaning
process. In addition, an apparent relationship was demonstrated between the
AFES intervention periods and the change in ventilatory parameters and SBT
duration. Although these results have to be taken with the necessary caution
for a single case study, they provide compelling data to support the hypothesis
that AFES can be used to assist with weaning in tetraplegic SCI. The results in
this study provide the necessary justification for future follow up work in a larger
subject cohort.

Chapter 8

Automatic Timing of AFES

8.1 Introduction

The effects of AFES applied over a period of several weeks on the respiratory function of tetraplegic patients was investigated in the two clinical studies that were completed for this thesis. During the AFES training sessions in these studies, either the researcher attempted to synchronise the stimulation with the patients volitional breathing (Chapter 3), or the patient was instructed to synchronise their volitional breathing with a pre-determined stimulation pattern (Chapter 7). There are two disadvantages with these systems:

1. The patient's breathing may not remain synchronised with the stimulation.

2. Either the researcher or the patient is required to monitor the stimulation output.

An automatic stimulation triggering system was used in the first clinical study of this thesis, which was based on the work by Gollee et al. [57], and is described in Chapter 3. In quiet breathing mode, this system monitored the patient's volitional breathing using a spirometer and applied stimulation automatically in synchrony with a patients exhalation. However, the use of a spirometer required the patient to wear a face mask which is impractical for a device that is used regularly in the clinic.

Spivak et al. [133] proposed an alternative approach for automatic control of stimulation, which used electromyography measurements of muscle activity as a trigger for AFES. Electromyography measurements were taken from the pectoral muscles, however these muscles are only functional during cough and only active in lower level tetraplegic SCI [144]. Therefore, this approach would not be suitable as a method of triggering AFES in synchrony with quiet breathing.

There have been other studies that have concentrated specifically on suitable sensors for timing of AFES [55,60], while using a triggering system similar to that described by Gollee et al [57]. Gollee and Chen [55] used an inertial measurement unit attached to a belt around the abdomen. While the results of this study showed that an inertial measurement unit could be suitable for use as a sensor for timing of stimulation, it would be sensitive to other body movements as well as those produced by breathing.

Gollee and Mann [60] used piezoelectric effort belts worn around the chest and the abdomen to measure breathing. This study showed the feasibility of this type of sensor for timing AFES-assisted breathing. However the system was only tested in two tetraplegic subjects and therefore needs to be further validated.

In order to be able to assess different AFES systems, their performance needs to be quantified. In previous work this has either not been reported [132], or been reported only qualitatively [57]. The primary function of an AFES system is to provide stimulation to the abdominal muscles in synchrony with exhalation. Moreover, stimulation applied during inhalation may increase the work of breathing. Therefore, an ideal AFES system should not fail to stimulate during exhalation, it should not stimulate during inhalation, and there should be no phase delay between the start of exhalation and the start of stimulation. Furthermore, these AFES system characteristics should remain consistent over several days of use, through a range of breathing rates and volumes, and while the patient is either active or inactive. Finally, an ideal system should not need to be calibrated for individual patients.

Based on the clinical data collected in this thesis and the disadvantages associated with previous work described above, the aim of the study presented in this chapter was to develop and validate a new, practical respiratory sensor and algorithm combination that would allow AFES to be synchronised automatically with a patient's volitional breathing pattern.

8.2 Objectives

The objective of this study was to design a non-invasive stimulation triggering system with a sensitivity, error rate and phase shift that was comparable to a spirometer based stimulation system and that was:

1. Robust to variations in breathing rate and volume.

2. Robust to movement not related to breathing.

3. Robust between days of use.

8.3 Methods

8.3.1 Subjects

This study involved ten able-bodied subjects who were in good general health and who were not pregnant. Of the subjects who were recruited, six were male and four were female. No subjects were past or present smokers. All procedures were approved by the Faculty of Biomedical and Life Sciences ethics committee, University of Glasgow.

8.3.2 Apparatus

A modified version of the apparatus used in the first clinical study of this thesis (described in Chapter 3) was used to apply stimulation to the abdominal wall muscles in synchrony with exhalation, record all sensor data, and provide a GUI for the experiments.

The subject's air flow rate was measured at the mouth using the spirometer described in Section 3.2.2. In addition, the subject's breathing was monitored using a nasal/oral thermocouple (Pro-Tech, USA) and chest and abdominal movements were measured using two piezoelectric belts (Pro-Tech, USA). The typical outputs of the thermocouple and piezoelectric belts during quiet breathing were $300 \ \mu V$ and $1 \ mV$ respectively. An instrumentation amplifier [98] was used to amplify, and to apply a 15 Hz low pass filter to, the thermocouple and piezoelectric belt outputs before they were digitised by a data acquisition card (6036E, National Instruments, Texas, USA). A potentiometer and a push button switch were used to control the output of the stimulator; their outputs were digitised using the data acquisition card. The data acquisition card was connected to a laptop PC, which ran the system control algorithm in Simulink (Mathworks, Massachusetts, USA) and controlled the output of the stimulator (described in Section 3.2.1). The GUI described in Section 3.3 was modified to include the output of the piezoelectric belts and the thermocouple and was displayed on the laptop's built in monitor. In addition an external monitor was used to display a second biofeedback GUI (described in Section 8.3.4). A block diagram of the system setup is shown in Figure 8.1.

The complete control algorithm described in Section 3.3 was used to control the output of the stimulator, however this experiment only used the system's
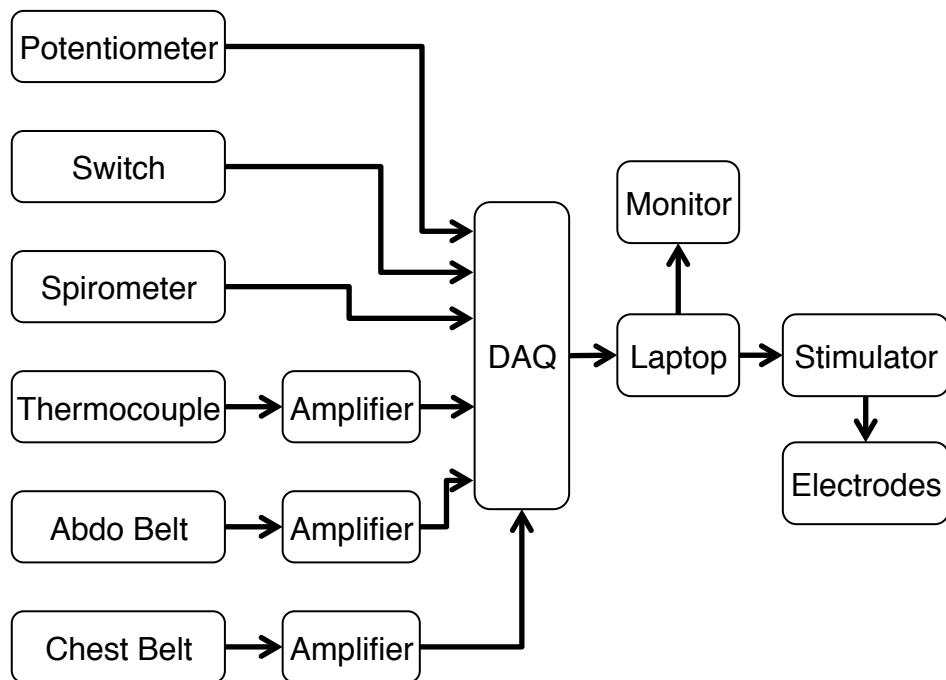
Figure 8.1: Block diagram of the experimental system. DAQ: data acquisiton card; Abdo Belt: abdominal belt.

quiet breathing stimulation mode. The complete Simulink model used in the experiment is shown in Appendix A.

8.3.3 Apparatus Setup

The stimulation electrodes were placed on the abdomen as shown in Figure 3.2 (page 53). The stimulation frequency was set at 30 Hz and the stimulation pulse width was filtered using a second order transfer function with a 0.1 s rise time for all tests in this experiment. The current for each channel of stimulation was adjusted until a strong, visible contraction of the corresponding muscle group was observed at a constant pulsewidth of 150 μs. Following this, stimulation was applied to all channels simultaneously, and adjustments were made to the current settings for each channel, until an even contraction across the abdomen was obtained. Since transcutaneous stimulation recruits sensory as well as motor nerves, care was taken throughout this process to ensure that no discomfort was caused to the subject. The stimulation parameters in this studies were chosen based both on the settings used in the previous studies.

The abdominal belt was placed so that the centre of the piezoelectric material covered the subject's naval. The chest belt was placed so that the centre of the

piezoelectric material was inline with the base of the sternum. Both of the belts were affixed so that the piezoelectric sensor measured approximately 12 cm at the end of normal exhalation.

The thermocouple was placed on the upper lip so that the nasal sensing probes were just below the nostrils and the oral sensing probe was in line with the middle of the lips. The thermocouple was held in place by tightening the cable around the back of the subject's head.

The face mask was secured using a net that was placed around the back of the subject's head and clipped on to both sides of the face mask. The net was tightened to ensure that there were no leaks from the mask.

Prior to the start of the study the calibration of the spirometer was verified using a three liter calibration syringe as described in Section 3.2.2; the piezoelectric belts and thermocouple were not calibrated. Several trial runs of the study protocol were completed before the start of formal data collection to ensure that the system functioned as designed and that the study protocol ran smoothly.

8.3.4 Study Protocol

This study included two assessment sessions which were conducted on two separate days. After the apparatus was set up as described in Section 8.3.3 the subject was asked to perform a series of unassisted and AFES-assisted breathing exercises. In total there were nine different breathing exercises. Each assessment session included three sets of the nine breathing exercises as illustrated in Figure 8.2 .
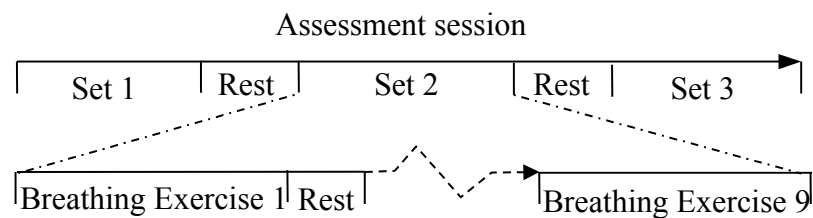
Figure 8.2: Outline of the assement protocol

Within a set the order of the breathing exercises was randomised. Subjects were allowed to rest for as long as they wished between breathing exercises. The different breathing exercises are described below.

Unassisted QB Subjects were asked breathe as normally as possible for one minute. Subjects were given no feedback on their breathing pattern.

AFES QB Similar to unassisted QB except that the subject's breathing was assisted with AFES. Subjects were instructed not to focus on their breathing or the sensation of stimulation.

Unassisted deep breathing Subjects were instructed to breathe with double their average unassisted QB V_T for 30 seconds. A GUI gave the subjects real-time feedback on the volume of the current breath and displayed a target breath volume range (Figure 8.3(a)). The range was set to be $\pm 10\%$ of target tidal volume. Subjects were instructed to breathe as continuously and as smoothly as possible during this exercise.

AFES deep breathing Similar to unassisted deep breathing except that the subject's breathing was assisted by AFES.

Unassisted rapid breathing Subjects were instructed to breathe at double their average unassisted QB BR for 30 seconds. During this exercise a GUI displayed a white circle with twelve equally spaced markings (similar to a clock face without numbers). A large red dot moved round the outer edge of the circle with a period that was equal to the reciprocal of the target breathing rate. Subjects were instructed to complete a full breathing cycle (i.e. inhalation and exhalation) in synchrony with one revolution of the red dot (Figure 8.3(b)). Subjects were asked to try to breathe as smoothly as possible during this exercise.

AFES rapid breathing Similar to unassisted rapid breathing except that the subject's breathing was assisted by AFES.

No breathing In this exercise subjects were asked to hold their breath for 15 seconds.

No breathing with hand clapping In this exercise subjects were asked to hold their breath for 15 seconds while clapping their hands above their head.

Quiet breathing with hand clapping In this exercise subjects were asked to clap their hands above their head while breathing as normally as possible. This breathing exercise lasted for 15 seconds.

(a) Deep breathing GUI   (b) Rapid breathing GUI
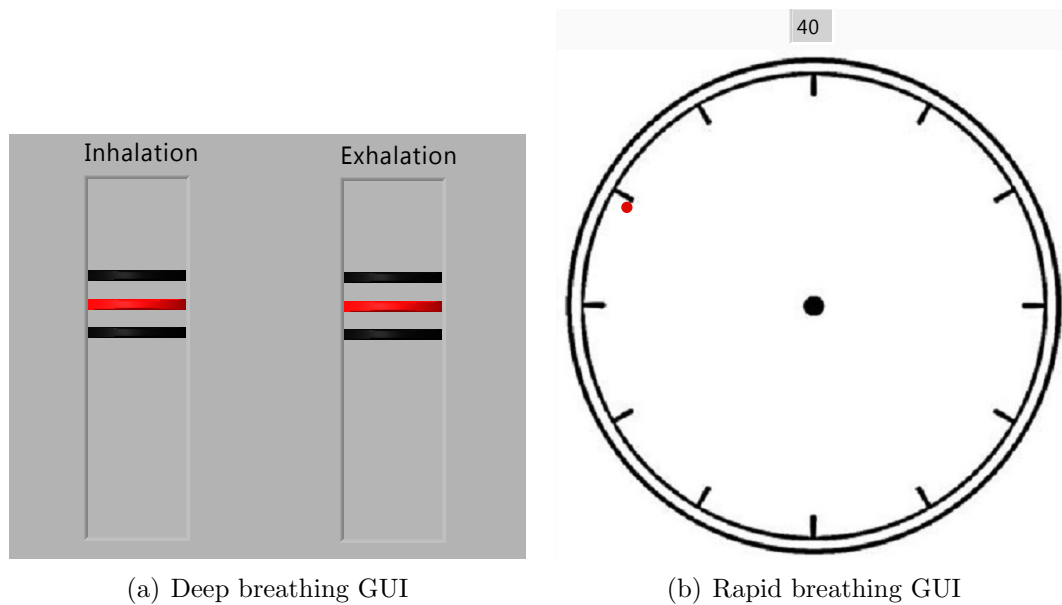
Figure 8.3: The GUIs used for the deep breathing and rapid breathing tests. (a) shows the GUI used during the deep breathing tests. The red bar indicates the volume of the current inhalation or exhalation. Subjects were instructed to modify their V_T so that at the end of each inhalation or exhalation the red bar was between the black tolerance bars. (b) shows the GUI used during the rapid breathing test. The red dot travelled around the clock face at the target breathing rate which is shown in breaths per minute at the top of the clock face. Subjects were instructed to complete a breathing cycle (inhalation and exhalation) in synchrony with the red dot making a complete rotation of the clock face.

8.3.5   Data Screening

Sets of breathing exercises were visually inspected for each breathing sensor. If there had been a problem recording the data from any of the breathing exercises then this data was removed. Typical problems included the sensor becoming displaced and the sensor becoming disconnected. An example of recorded thermocouple data that was removed due to the sensor becoming displaced is illustrated in Figure 8.4

8.3.6   Algorithm Development

For each assessment session the data recorded over the three sets of breathing exercises was combined into a single data set to give a data set for each sensor per breathing exercise.

The location of the air flow rate zero crossings corresponding to the start of inhalation and exhalation were calculated from the output of the spirometer as described in Section 3.7.1.
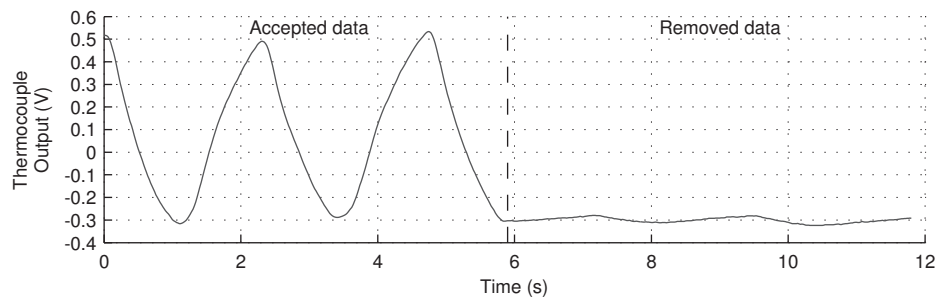
Figure 8.4: An example of the change in the thermocouple signal when the thermocouple became dislodged.

The analysis of the recorded signals from each of the other breathing sensors was divided into the following steps (i) feature identification, (ii) filtering, (iii) development of a feature detection algorithm, (iv) matching the detected features to the corresponding zero crossings, and (v) evaluation

Feature Identification

Feature identification involved identifying the points in the signals recorded by the alternative sensors (abdominal belt, chest belt, and thermocouple) which corresponded to the start of exhalation and inhalation as measured by the spirometer. This was done by comparing visually the output from each of the alternative sensors to the air flow rate measured by the spirometer. As illustrated in Figure 8.5 the peaks and troughs in the thermocouple output approximately corresponded to the start of exhalation and inhalation respectively. For the belt signals the mid point between a trough and a peak corresponded to the start of exhalation, while the mid-point between a peak and a trough corresponded to the start of inhalation.

Filtering

The recorded thermocouple signal contained a small amount of noise, which according to its frequency response was not specific to a single frequency. A range of simple moving average filters with different window types and filter orders were tested. A 5th order simple moving average filter with a gaussian window was selected since it provided sufficient smoothing with a minimal phase delay.

It was necessary to remove the offset in the recorded piezoelectric belt signals so that a zero crossing algorithm could be written to detect the location of inhalation and exhalation in the signals. A range of infinite impulse response high pass filters were tested. A 1st order Butterworth high pass filter with a 0.08 Hz 3
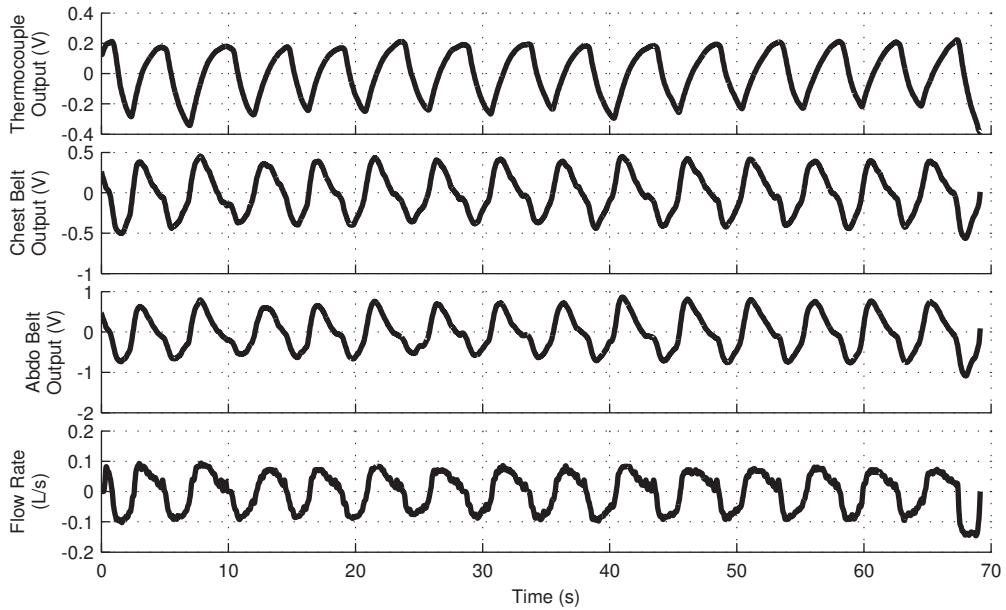
(a)

Figure 8.5: Comparison of air flow rate measured by the spirometer and the output of the thermocouple and piezoelectric belts. The outputs from each of the sensors were filtered as described in Section 8.3.6.

dB cutoff was selected as it adequately removed the offset with a minimal phase delay.

Feature Detection Algorithms

For the piezoelectric belts a zero crossing algorithm was developed and for the thermocouple a peak and trough detection algorithm was developed. Both algorithms were developed so that they could be used in an online system to detect the onset of exhalations and inhalations.

Zero Crossing Detection   Zero crossings were considered as the points at which the sign of the signal changed either from negative to positive (exhalation), or from positive to negative (inhalation). In the algorithm developed an exhalation (inhalation) was defined:

1. IF the number of positive (negative) samples was greater than the number of negative (positive) samples in the window of length FW_E (FW_I), after the current point AND the number of negative (positive) samples was greater than the number of positive (negative) samples in the window of length BW_E (BW_I) before the current point.

2. AND the last detected zero crossing was not an exhalation (inhalation).

3. AND the integral between the last zero crossing and the current point was greater than Int_E (Int_I).

4. AND EITHER the period between the last zero crossing and the current point was greater than $Blank_E$ ($Blank_I$) multiplied by the period between the previous pair of zero crossings OR the period between the last zero crossing and the current point was greater than five seconds.

Condition two in the above algorithm was to mitigate false positives that were caused by small signal excursions over the zero crossing which were not related to breathing. In condition four the first statement was to mitigate false positive zero crossings caused by large troughs that crossed zero at the onset of stimulation (see Figure 8.6). The second statement acted as an algorithm reset when the algorithm had failed to identify one or more previous zero crossings. Five seconds was chosen based on the slowest expected breathing rate of a user, which was taken as six breaths per minute.[1]

Peak and Trough Detection   Peaks and troughs were considered by examining the gradient of the samples in windows either side of an expected peak or trough. In the algorithm developed a peak (trough) was defined:

1. IF the difference between each of the samples, in the window, of length BW_E (BW_I), leading up to the peak (trough) was greater (less) than or equal to zero AND the difference between the samples, in the window, of length FW_E (FW_I), following the peak was less (greater) than or equal to zero.

2. AND the last detection was not a peak (trough).

3. AND the integral between the previous trough (peak) and the current point was greater than Int_E (Int_I).

4. AND EITHER the period between the current peak (trough) and the previous trough (peak) was greater than $Blank_E$ ($Blank_I$) multiplied by the period between the previous trough (peak) and the previous peak (trough) OR the period between the previous trough (peak) and the current point was greater than five seconds.

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[1]Each pair of zero crossings is equivalent to half a breath cycle, therefore the threshold of five seconds represents a full breath cycle lasting 10 seconds; or equivalently a breathing rate of six breaths per minute
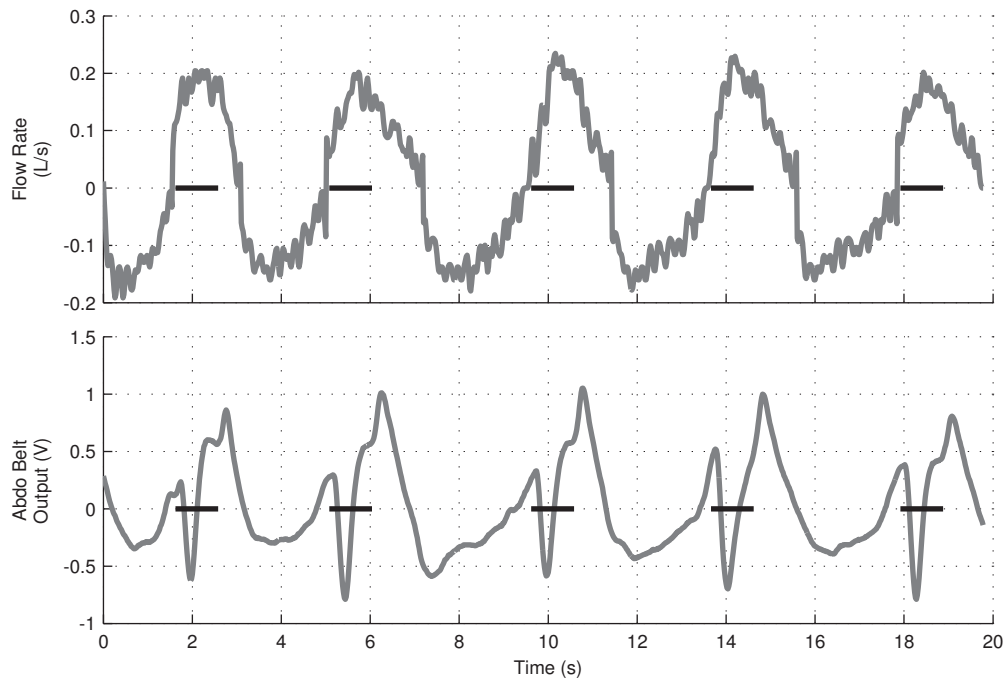
Figure 8.6: Example of the stimulation artefact that occured during the early phase of expiration in the abdominal belt output. The upper plot shows the flow rate and the lower trace shows the abdominal belt output. In both plots, the horizontal black bars show the period that stimulation was active.

Matching Flow Rate Zero Crossings to Detected Features

Each of the zero crossings detected in the airflow rate were matched to the closest feature detected by each of the alternative sensors according to the following rules:

1. An exhalation detected in the airflow rate could only be matched to a feature that corresponded to an exhalation detected in the alternative sensor. For example, a negative to positive zero crossing in the flow rate measured by the spirometer could only be matched to a trough in the thermocouple signal. An equivalent rule was followed for inhalations.

2. Zero crossings detected in the airflow rate could only be matched with features detected in the signal from the alternative sensor that occurred within half of the average breathing period before or after the airflow rate zero crossing.

It should be noted that for this analysis the sample at the end of the window after the alternative sensor breath feature (i.e. the sample at the end of FW_E or FW_I) was used, since this is the earliest sample at which the breath feature could be detected in an online system.

Evaluation

The outcome measures that were used to assess the difference between the exhalations and inhalations detected using the spirometer and the exhalations and inhalations detected using the alternative breathing sensors were sensitivity, error rate and phase shift.

Sensitivity   True positives (TP) were defined as exhalations or inhalations that were detected by both the alternative breathing sensor and the spirometer. The total number of breaths (N_B) was defined as the total number of breaths detected by the spirometer. Accordingly, sensitivity was defined according to Equation 8.1.

$$Sensitivity = \frac{TP}{N_B} * 100 \tag{8.1}$$

The reciprocal of sensitivity is the false negative (FN) rate, where false negatives were defined as exhalations or inhalations that were not detected by the alternative breathing sensor but were detected by the spirometer.

Error Rate   False positives (FP) were defined as exhalations or inhalations that were detected by the alternative breathing sensor but not detected by the spirometer. Accordingly error rate was defined according to Equation 8.2.

$$Error\ rate = \frac{FP}{N_B} * 100 \tag{8.2}$$

Phase Shift   Phase shift was defined as the number of samples between the alternative sensor true positives and the corresponding inhalations or exhalations detected by the spirometer. A positive phase shift indicated that the exhalation or inhalation detected by the alternative sensor occurred after the exhalation or inhalation detected by the spirometer.

Algorithm Parameter Optimisation

To find the optimal set of parameters (BW_E, BW_I, FW_E, FW_I, Int_E, Int_I, $Blank_I$ and $Blank_E$) for a given sensor and algorithm combination a parameter sweep routine was written and performed in Matlab. The routine calculated the sum of the number of false positives and false negatives during AFES quiet breathing, deep breathing, and rapid breathing on assessment one using a range of values of each algorithm parameter (determined empirically and shown in Table 8.1) for a given algorithm and sensor combination. The combination of parameters that

reduced the sum of the false positives and the false negatives for a given sensor and algorithm combination were considered to be optimal.

The optimal set of parameters were calculated on an individual subject basis and on the pooled subject data. Since the overall group mean sensitivity and error rate was not significantly different when using the individual subject set of optimal parameters and the global set of optimal parameters, the global set of optimal parameters were used for the remainder of the data analysis.

Table 8.1: The range of algorithm parmaters tested in the parameter sweep for each algorithm and sensor combination.

Parameter	Sensor (lower limit, upper limit, increment)		
	Abdo belt	Chest belt	Thermocouple
BW_I, BW_E	1, 10, $\Delta 1$	1, 10, $\Delta 1$	0, 10, $\Delta 1$
FW_I, FW_E	1, 10, $\Delta 1$	1, 10, $\Delta 1$	0, 10, $\Delta 1$
Int_I, Int_E	0, 0.15, $\Delta 0.01$	0, 0.15, $\Delta 0.01$	2, 3.5, $\Delta 0.1$
$Blank_I, Blank_E$	0.1,0.9,$\Delta 0.1$	0.1,0.9,$\Delta 0.1$	0.1,0.9,$\Delta 0.1$

8.3.7 Statistics

Statistics were calculated on the group results pooled over all of the subjects. The pooled results were tested to see whether they followed a normal distribution using the Shapiro-Wilks test. It was found that while some of the pooled results followed a normal distribution, for example the phase shift results, other results did not. Therefore, for consistency, all statistical comparisons were performed using non-parametric tests. Paired comparisons were performed using the Wilcoxon rank sum test. Intra subject comparisons of three or more groups were performed using the Friedman test. Post-hoc multiple comparison testing using the Tukey-Kramer Honestly Significant Difference criterion was used when a significant difference was detected using the Friedman test. The statistical significance level was set at $p < 0.05$.

8.4 Results

8.4.1 Algorithm Parameters

The globally optimal algorithm parameters determined from the parameter sweep are shown in Table 8.1.

The overall mean sensitivities and error rates calculated from the pooled AFES quiet breathing, deep breathing and rapid breathing (collectively, AFES-B) data

Table 8.2: The globally optimal algorithm parameters determined from the parameter sweep of the AFES-B data from assessment one.

Parameter	Sensor		
	Abdo belt	Chest belt	Thermocouple
FW_I	3	1	5
BW_I	1	1	0
$Blank_I$	0.4	0.4	0.3
Int_I	0.1	0.03	3
FW_E	1	1	7
BW_E	1	1	0
$Blank_E$	0.3	0.3	0.3
Int_E	0.1	0.08	0

from both assessment sessions using the globally optimised parameter set were not significantly different from those calculated using the individual subject optimised parameter sets (Table 8.3). For the same comparison the phase shift was not significantly different for the abdominal belt, and the chest belt but it was significantly different for the thermocouple (Table 8.3). The phase shift of the thermocouple system using the globally optimised parameters was $0.02 \pm 0.07s$, whereas the equivalent phase shift calculated using the individually optimised parameters was $0.08 \pm 0.08s$ (mean $\pm$ standard deviation).

Table 8.3: p-values obtained when the AFES-B results obtained using the globally optimised algorithm parameters were compared with the equivalent results obtianed using the individually optimised algorithm parameters.

Outcome	Sensor		
	Abdo belt	Chest belt	Thermocouple
Sensitivity	0.33	0.31	0.19
Error rate	0.64	0.5	0.19
Phase shift	0.49	0.10	<0.01

8.4.2   Overall Performance

The mean sensitivities of the pooled AFES quiet breathing, deep breathing and rapid breathing results, taken over both assessment sessions for individual subjects, are illustrated by box plots for each of the alternative sensors in Figure 8.7(a). Similarly the error rate and phase shift results are shown in Figures 8.7(b) and 8.7(c) respectively.

Friedman testing found a significant difference in the sensitivity and error rate of each of the sensors ($p < 0.01$ and $p = 0.01$ respectively). Multiple comparison

(a) Sensitivity

(b) Error Rate

(c) Phase Shift
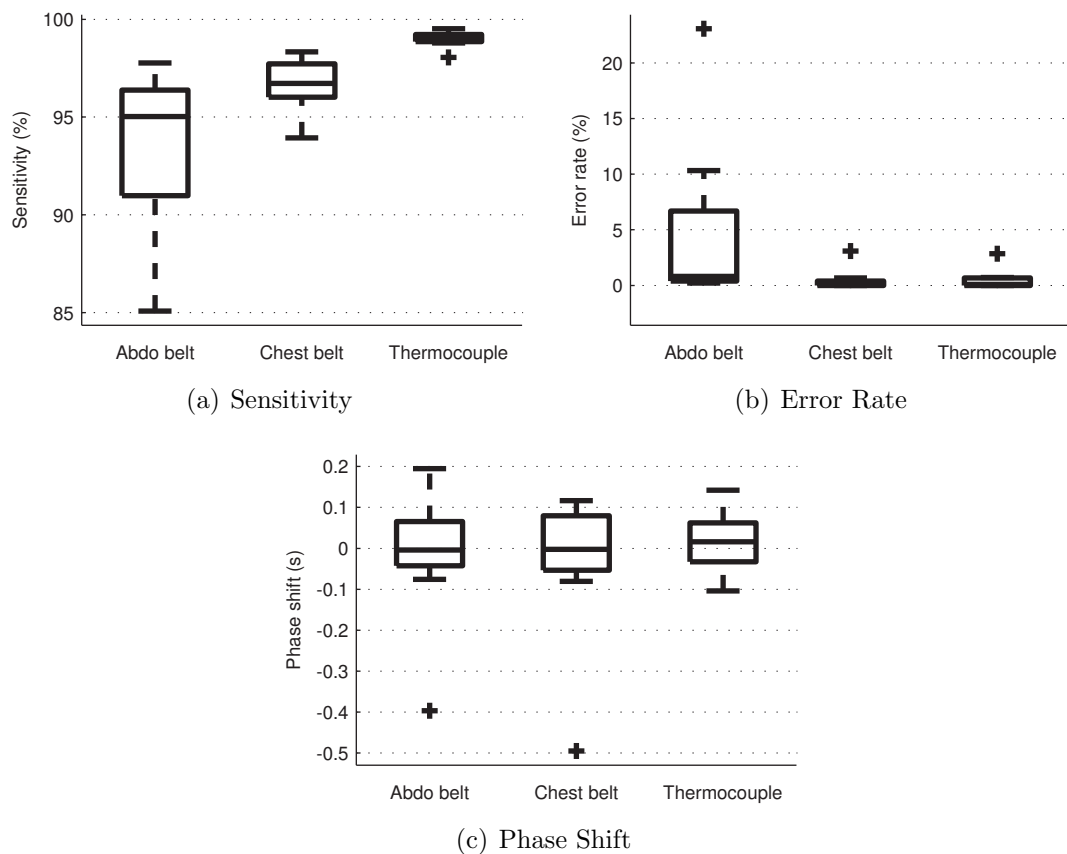
Figure 8.7: Box plots showing the overall performance of each of the alternative sensors during AFES-assisted breathing. Results were calculated by pooling the quiet breathing, rapid breathing and deep breathing over both assessment sessions. In each box plot, the middle bar represents the median, the box edges represent the upper and lower limit of the interquartile range, the whiskers represent the complete spread of the data (excluding outliers) and the crosses represent outliers. Outliers were defined as points that were either above the 75th percentile or below the 25th percentile by a factor of one and a half times the interquartile range.

testing found that the sensitivity of the thermocouple system was significantly greater than the sensitivity of both the abdominal belt and chest belt systems. In addition the error rates for the thermocouple and chest belt systems were significantly lower than the abdominal belt system error rate. There was not a significant difference in phase shift ($p = 0.17$) between the sensors.

8.4.3 Repeatability

For all three of the alternative sensors, the sensitivity, error rate and phase shift did not differ significantly between the assessment sessions. The p-values from the comparisons are given in Table 8.4

Table 8.4: p-values from the comparison between assessment session one and assessment session two using the Wilcoxon rank sum test. For the comparisons the mean sensitivity, error rate and phase shift was calculated from the pooled AFES quiet breathing, rapid breathing, and deep breathing.

	Sensitivity	Error rate	Phase shift
Thermocouple	0.23	1	0.69
Chest belt	0.50	0.44	0.28
Abdo belt	0.92	0.91	0.23

8.4.4 Effect of Breathing Pattern

The mean sensitivities, error rates, and phase shifts, taken over both assessment sessions for individual subjects, for AFES quiet breathing, deep breathing, and rapid breathing are illustrated by box plots in Figure 8.8.

The effect of the breath pattern on the sensitivity of the thermocouple system was statistically significant ($p = 0.02$) whereas for both the abdominal and chest belt systems the effect was not significant ($p = 0.41$ for both systems). Post-hoc multiple comparison testing found that AFES deep breathing was significantly different to AFES-QB for the thermocouple system.

Error rate was not significantly affected by breathing pattern for either the thermocouple ($p = 0.56$), or the chest belt ($p = 0.24$) or the abdominal belt ($p = 0.70$) systems.

The phase shift of each of the alternative sensor systems was affected by the breathing pattern ($p < 0.01$ for both the thermocouple and chest belts systems, and $p = 0.01$ for the abdominal belt system). Multiple comparison testing found that the phase shift was significantly different between:

- AFES rapid breathing and AFES-QB for the thermocouple system;

- AFES deep breathing and AFES rapid breathing for the abdominal belt system;

- AFES rapid breathing and both AFES-QB and AFES deep breathing for the chest belt system.
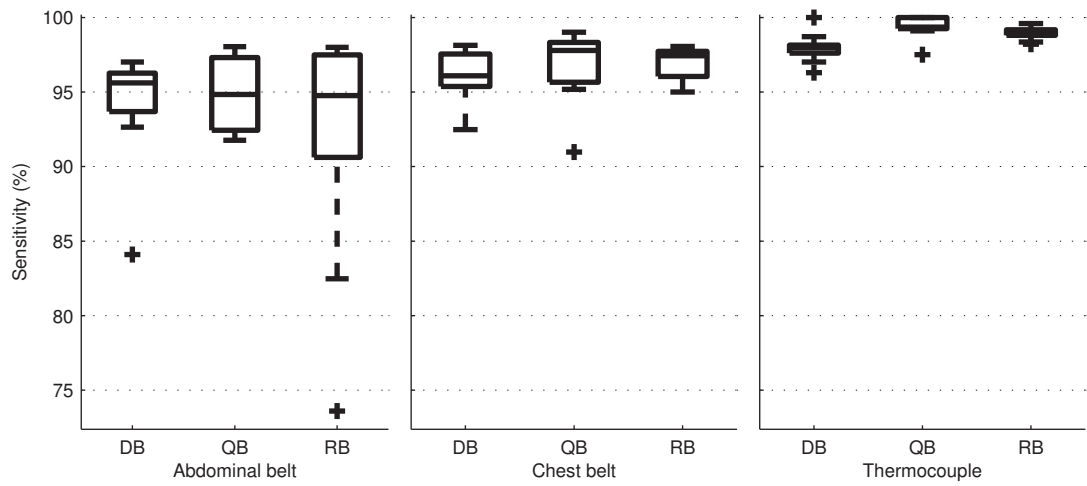
(a) Sensitivity
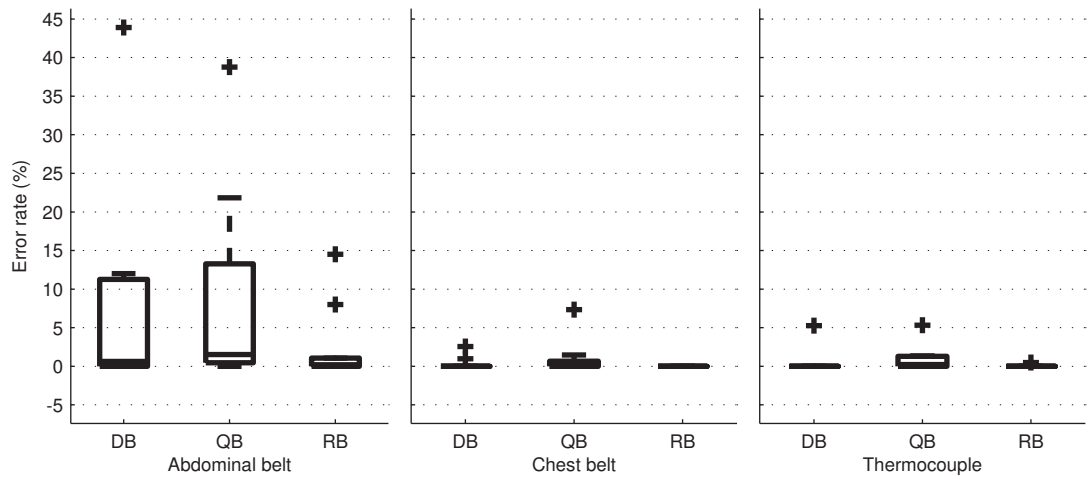
(b) Error Rate
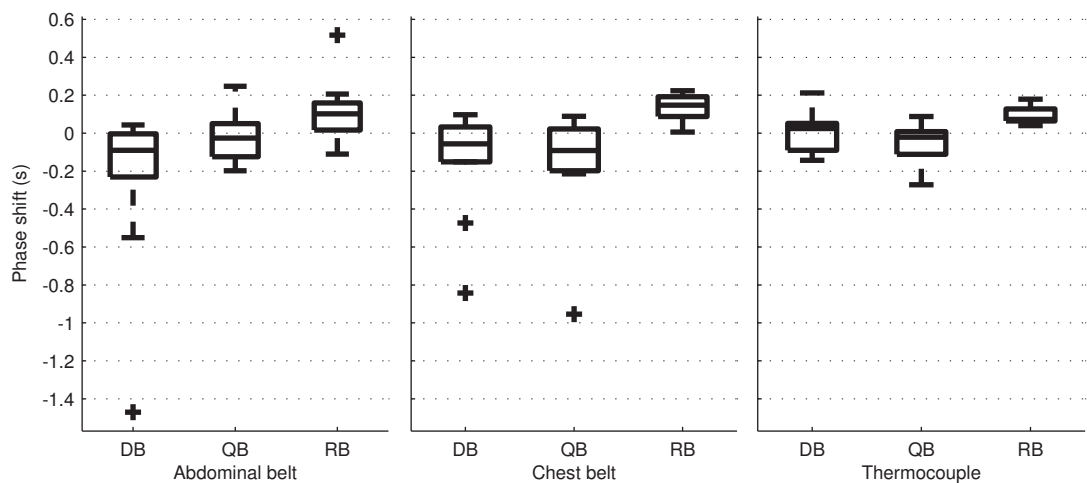
(c) Phase Shift

Figure 8.8: Effect of breathing pattern on the performance of the systems. The results were calculated by pooling the data over both assessment sessions. In each box plot, the middle bar represents the median, the box edges represent the upper and lower limit of the interquartile range, the whiskers represent the complete spread of the data (excluding outliers) and the crosses represent outliers. Outliers were defined as points that were either above the 75th percentile or below the 25th percentile by a factor of one and a half times the interquartile range.

8.4.5 False Positives During Periods of No Breathing

Example output from each of the sensors during a period of no breathing is shown in Figure 8.9.
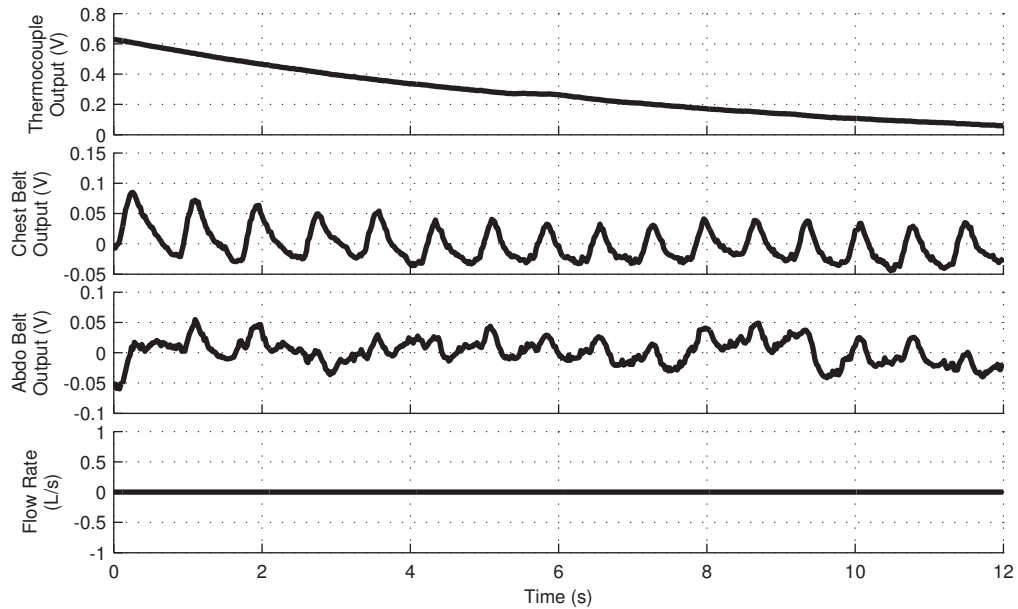
Figure 8.9: Example output from each of the sensors during a period of no breathing.

The number of false positives which occurred during periods of no breathing are illustrated by box plots for each of the respiratory sensors in Figure 8.10. For each sensor system the number of false positives was significantly greater than zero ($p < 0.01$ for each of the systems).
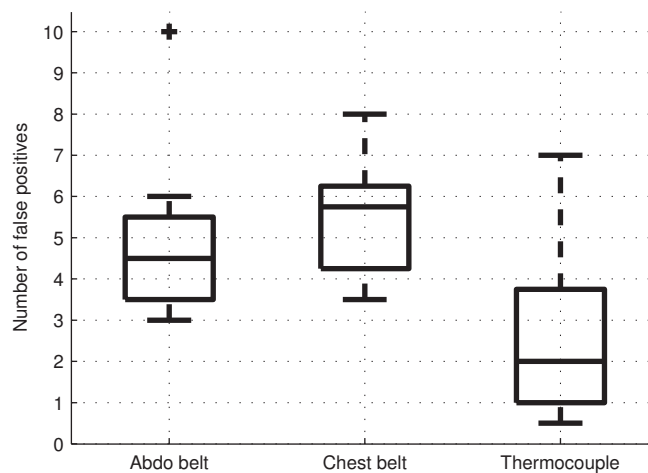
Figure 8.10: Number of false positives that occurred during periods of apnea. Results were calculated using pooled no breathing data from both assessments. In each box plot, the middle bar represents the median, the box edges represent the upper and lower limit of the interquartile range, the whiskers represent the complete spread of the data (excluding outliers) and the crosses represent outliers. Outliers were defined as points that were either above the 75th percentile or below the 25th percentile by a factor of one and a half times the interquartile range.

8.4.6 Effect of Movement Unrelated to Breathing

Figure 8.11 shows the effect of hand clapping on the output from the alternative sensors during a period of no breathing (Figure 8.11(a)) and during a period of quiet breathing (Figure 8.11(b)).

The number of false positives during period of no breathing with hand clapping for each sensor system is illustrated by box plots in Figure 8.12(a). The sensitivities, error rates and phase shifts during periods of unassisted QB and quiet breathing with hand clapping for each of the alternative sensor systems are illustrated by box plots in Figures 8.12(b), 8.12(c) and 8.12(d) respectively.

The statistical analysis found the following:

- The number of false positives during periods of no breathing with hand clapping was significantly greater than the number of false positives during periods of no breathing for each of the sensor systems ($p < 0.01$ in all cases).

- The unassisted QB and quiet breathing with hand clapping sensitivities were significantly different for each of the alternative sensor systems ($p < 0.01$ in all cases).

- The unassisted QB and quiet breathing with hand clapping error rates were significantly different for the abdominal belt system ($p = 0.02$) but not for the thermocouple system ($p = 0.16$) or the chest belt system ($p = 0.05$).

- The unassisted QB and quiet breathing with hand clapping phase shifts were significantly different for the thermocouple ($p < 0.01$), chest belt ($p < 0.01$) and abdominal belt ($p = 0.02$) systems.
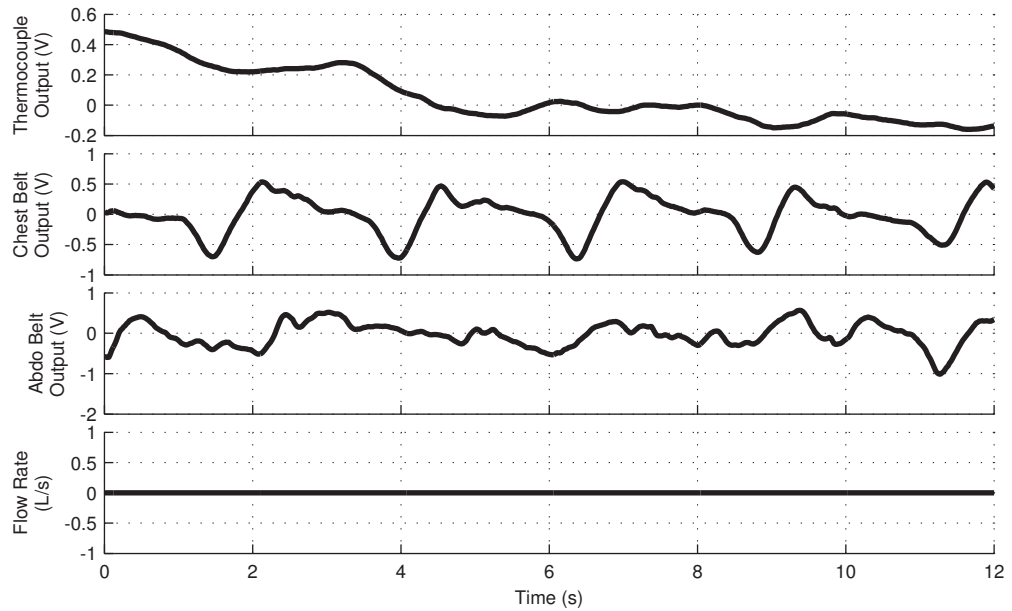
(a) NBHC
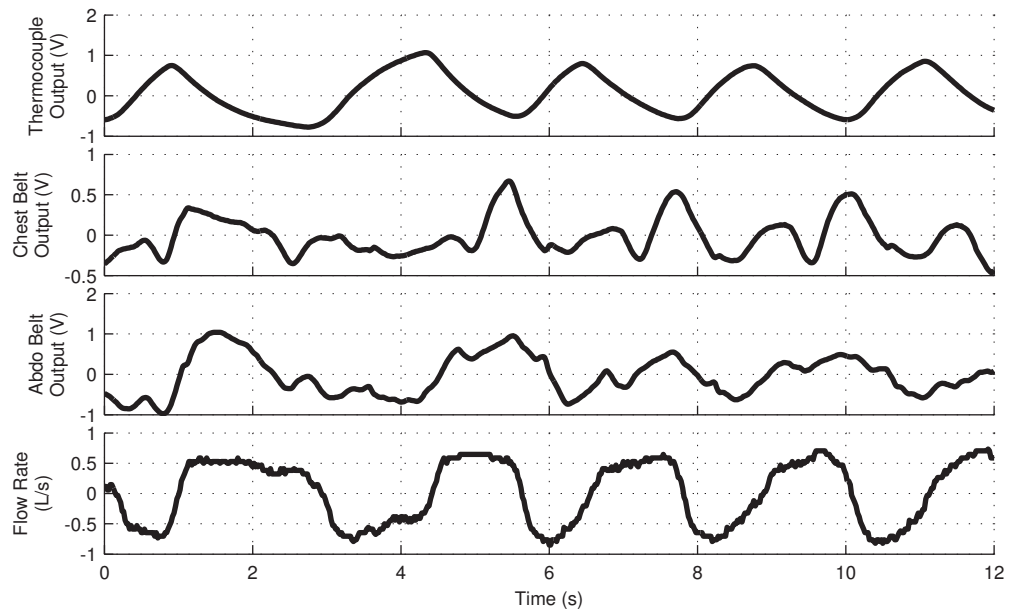
(b) QBHC

Figure 8.11: Example outputs of the sensors during (a) no breathing with hand clapping and (b) quiet breathing with hand clapping.
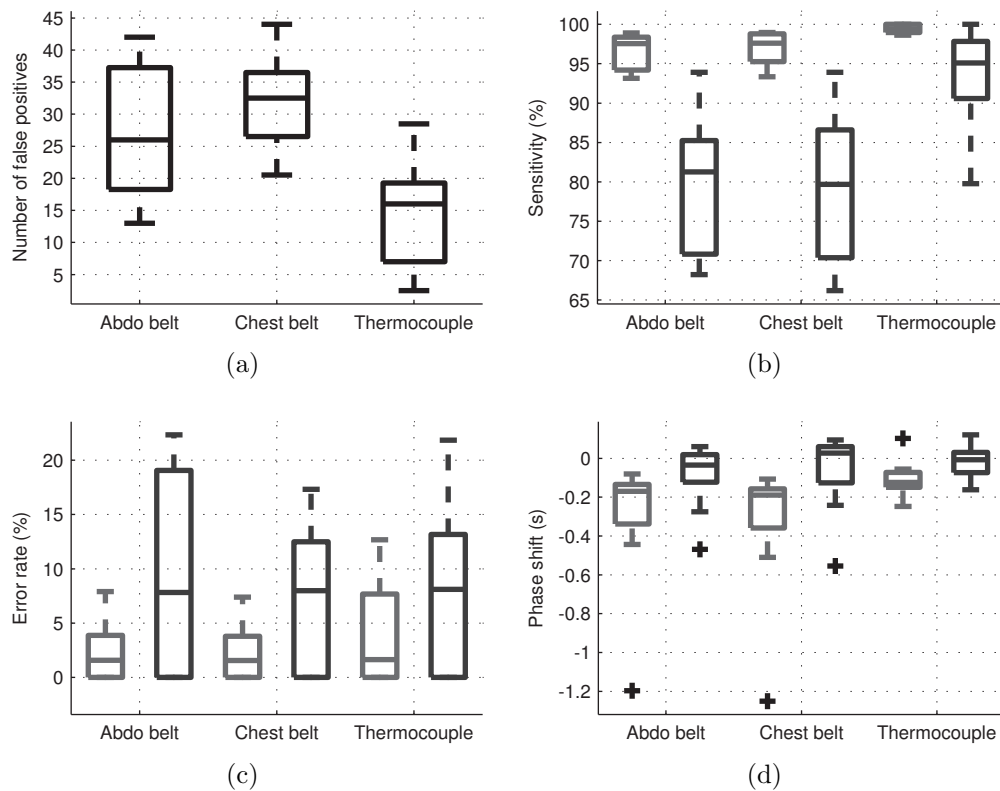
Figure 8.12: The effect of movement unrelated to breathing on the performance of the three systems. (a) shows the number of false positives generated by hand clapping during a period of apnea. (b) - (d) compares the sensitivity, error rate and phase shift between Unassisted-QB (grey boxes) and quiet breathing with hand clapping (black boxes). In all of the plots the results were calculated based on the pooled data from both assessment sessions. In each box plot, the middle bar represents the median, the box edges represent the upper and lower limit of the interquartile range, the whiskers represent the complete spread of the data (excluding outliers) and the crosses represent outliers. Outliers were defined as points that were either above the 75th percentile or below the 25th percentile by a factor of one and a half times the interquartile range.

8.5 Discussion

The aim of this study was to develop a new respiratory sensor and algorithm combination suitable for triggering AFES in synchrony with a patient's volitional exhalation.

In this study three new systems were designed. The first system used a nasal and oral thermocouple in combination with a peak detection algorithm. The second and third systems both used piezoelectric belts in combination with a zero crossing algorithm. In the second system the belt was placed around the chest while in the third system the belt was placed around the abdomen. To evaluate the performance of the new systems, the inhalations and exhalation detected by

each of the new systems were compared to the inhalations and exhalation detected by the spirometer.

8.5.1 Sensitivity and Error Rate

The thermocouple and chest belt systems had significantly greater sensitivity and tended to have a smaller error rate than the abdominal belt system (Figure 8.7, page 162). For all subjects the thermocouple system sensitivity was greater than 98%, which was larger than either of the other two systems, and the error rate was less than 2%. On average these results equate to one missed breath and one unintentional burst of stimulation every three minutes[2].

The abdominal belt system's sensitivity was significantly reduced, and its error rate tended to be greater than either the thermocouple or the chest belt system (Figure 8.7, page 162). The most common explanation for this reduced performance was the stimulation artefact (see Figure 8.6, page 158) which was regularly present in the abdominal belt signal but not in either the thermocouple or chest belt signals. The zero crossing algorithm attempted to account for this artefact by incorporating a variable duration blanking window ($Blank_E$) after exhalation was detected. While this algorithm feature reduced false positives and false negatives for some subjects, it did not perform well for other subjects.

The sensitivity of the thermocouple system was reduced during periods of deep breathing compared with periods of either quiet breathing or rapid breathing (Figure 8.8, page 164). Neither the error rate of the thermocouple system nor the sensitivity and error rate of the abdominal and chest belt systems were affected by either breathing rate or breathing volume. Examination of individual subject cases found that the reduced thermocouple sensitivity during deep breathing was a result of unexplained noise in the signal rather than the mode of breathing. Collectively, these results show that the sensitivity and error rate of the three systems designed in this study are robust through a wide range of breathing patterns.

8.5.2 Phase Shift

The overall median phase shift for each of the alternative sensor systems was close to zero and ranged between -0.1 s and 0.1 s (Figure 8.7(c), page 162). The phase shift for each alternative sensor system was significantly affected by breathing pattern (Figure 8.8, page 164). For each sensor the phase shift during both deep

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[2]Assuming an average breath rate of 15 breaths per minute

breathing and quiet breathing tended to be similar and reduced compared with the phase shift during rapid breathing (Figure 8.8(c), page 164).

It was expected that while the phase shift of the abdominal and chest belts would be similar, since the abdomen and chest work in tandem to expand and compress the thorax [154], the phase shift of the belt signals would be less than zero and reduced compared with the thermocouple system for the following reasons:

1. The movement of air to and from the lungs begins with the expansion and compression of the thorax. In addition, previous authors have demonstrated that in measurements of abdominal and chest movement, using an inertial measurement unit [55] or respiratory inductive plethysmography belts [30], the zero crossings occur before the zero crossings in measured flow rate.

2. The thermocouple measures breathing activity by responding to a change in airflow temperature and there is an inherent phase delay between the change in temperature of the airflow and the change in output voltage produced by the thermocouple.

While the overall phase shift results (Figure 8.7(c)) contradict the above expectations, the analysis of the effect of breathing pattern on phase shift (Figure 8.8(c)) shows that the above expectations hold for deep breathing and quiet breathing. During rapid breathing the phase shifts become similar across the different alternative sensor systems and positive (compared with the spirometer system). In each of the alternative sensor systems, delays would be introduced through the analog and digital filtering process and the length of FW_I and FW_E chosen in the detection algorithms. In comparison, the spirometer provided a digital output of the flow direction, and therefore no filtering delays or algorithm delays were introduced into the system. Considering that the increased flow rate during rapid breathing compared with either quiet or deep breathing, is likely to have minimised the delay caused by the physical separation of the three alternative sensors and the spirometer, this would:

1. equalize the phase delay between each of the three alternative sensor systems, since the technical delay in each system was comparable and

2. increase the phase delay of each of alternative sensor systems compared with the spirometer, since the spirometer had minimal technical delay.

Practically speaking it is undesirable to have a stimulation triggering system that interrupts inhalation by applying stimulation before the start of exhalation

as this is likely to be uncomfortable for a patient and may lead to dyspnea. Although the phase delay of each of the alternative breathing systems was less than zero, this could be corrected for by adding an additional delay into the system. If AFES was being used for neuromuscular training the author believes that a small delay between the start of volitional exhalation and the onset of stimulation is of minimal concern. In comparison, if AFES was being used as a cough neuroprosthesis, the phase delay between the start of volitional exhalation and the onset of stimulation would be highly important as the greatest CPFs are reached during the beginning of exhalation. An additional usability factor that should be considered is that an inconsistent stimulation trigger may be distracting for the patient. In each of the systems designed in this study the phase shift changed between different modes of breathing. A future improved design could possibly correct for this difference by modeling the phase shift as a function of breathing pattern factors (e.g. BR, V_T, PEF etc.) and applying a variable delay to the system based on the predicted phase shift.

8.5.3 Effect of Apnea

All three of the systems designed in this study produced a statistically significant number of false positive detections during periods of apnea (Figure 8.10, page 166). However, the number of false positives detected tended to be largest for the abdominal and chest belt systems. As shown in Figure 8.9 the chest belt picked up a strong periodic signal during these periods, which was present to a lesser extent in the abdominal belt. It is presumed that this signal resulted from the heart beat of the subjects. Since heart beat frequency is greater than breathing frequency an improved design of the belt systems could include an analog filter with greater stop band attenuation or an additional low pass digital filter.

8.5.4 Effect of Movement Unrelated to Breathing

As shown in Figure 8.12 all three of the systems were affected by the subject clapping their hands over their head. The abdominal and chest belt systems were most severely affected by the hand clapping. As shown by Figure 8.11, the arm movement resulted in expansion and contraction of the chest that was unrelated to breathing. Although only a specific movement was tested in this study, these results illustrate a general limitation of the piezoelectric belt systems designed: the diameter of the abdomen and chest are affected by upper body movement in addition to breathing.

Figure 8.11(a) shows that the output of the thermocouple was affected by hand clapping during periods of apnea. A possible explanation is that small amounts of air escaped the nose or mouth during the exercise that was not detected by the spirometer.

As reported in Chapter 3, some patients included in the first clinical study of this thesis received AFES while they participated in hand therapy sessions. Therefore retained system performance during periods of upper body movement is an important property for an abdominal stimulation system that would be used in the clinic. In this regard, the thermocouple was least affected by arm movement and therefore the most suitable.

8.5.5 Practical Aspects

There was not a statistically significant difference between the results found in the two assessment sessions in this study. This indicates that the performance of the systems designed should be stable between different days of use.

The same algorithm parameters were used for every subject included in this study. It was found that the results obtained with these globally optimised parameters and the results obtained with individually optimised parameters were not statistically different. It is assumed that the globally optimised parameters would produce similar results in a wider tetraplegic population. This is a useful finding as it indicates a system which does not need to be specifically tuned for individual subjects.

All three sensors required minimal effort and were quick to apply to the subjects in this study. A disadvantage of either the abdominal or chest belt systems is that to place the belts the patient needs to lean forward, a feat which generally requires the assistance of two health care workers. In comparison the thermocouple could be placed on a tetraplegic patient as easily as it was placed on the healthy subjects in this study. The disadvantage of the thermocouple system is that it could not be used with a patient who had a tracheostomy.

8.5.6 Other Possible Sensors

There are a wide range of other respiratory sensors that are used currently in sleep studies. The most common of these are respiratory inductive plethysmography belts and systems that measure pressure changes in a nasal cannula.

Respiratory inductive plethysmography systems have generally superseded piezoelectric belt systems in the sleep market for two reasons:

1. The sensing element of the respiratory inductive plethysmography belt is effectively the whole belt whereas the sensing element of piezoelectric belts only covers a small region of the diameter of the belt. This means that respiratory inductive plethysmography belts are less susceptible to errors caused by parts of the belt becoming trapped when the patient moves.

2. Respiratory inductive plethysmography belts provide a more accurate measurement of volume.

Although respiratory inductive plethysmography belts have advantages over the piezoelectric belts, they are still likely to be susceptible to the movement artefacts caused by stimulation and by arm motion that were observed in the piezoelectric belt signal used in this study.

The shape of the waveform produced by the systems that measure pressure changes in a nasal cannula is closer to the flow rate signal measured be a spirometer, although it is not known whether this would result in improved performance when compared with the system by the thermocouple.

8.5.7   Study Limitations

The major limitation of this study was that the experiments were completed in healthy subjects and therefore these results have to be verified in tetraplegic patients. This is particularly important for the piezoelectric belt results as it is known that thoracic breathing mechanics can be affected in tetraplegia [154].

The methodology used to calculate the optimal algorithm parameters was limited in that the parameter sweep found the algorithm parameters that minimised the number of false positives and false negative but did not consider the phase delay.

8.6   Conclusions

The thermocouple system tended to have the greatest sensitivity, the lowest error rate and was least affected by arm movements compared with the abdominal and chest belts systems. Unless a patient has a tracheostomy, the thermocouple system should also be easiest to apply to patients compared with the other systems designed. Therefore, when AFES is used for pulmonary rehabilitation in spontaneously breathing tetraplegics this is the most suitable system from the three that were designed.

The performance of the chest belt was not statistically different to the performance of the thermocouple system when arm movement was not present. Since it is unlikely that patients would be completing other tasks that require arm movement while being weaned from MV, and the chest belt could be used in patients with a tracheostomy, the chest belt system designed in this study is recommended for triggering AFES automatically in interventions that are designed to improve weaning outcome in tetraplegic patients.

Chapter 9

Discussion:
The Role of AFES in Tetraplegia

Electrical muscle stimulation applications can be divided into two basic paradigms: neuromuscular retraining and neuroprosthetics [5]. In the context of this thesis, neuromuscular training refers to using AFES as a tool to improve a patient's unassisted respiratory function, whereas, an AFES neuroprosthesis uses stimulation to enhance a patient's respiratory function temporarily.

The results from previous research had indicated that AFES may be useful for neuromuscular training in tetraplegia [27, 87, 159]. However, these studies either combined an AFES intervention with other forms of respiratory muscle training [104, 159], or combined AFES with stimulation of additional muscle groups [87], leaving open the question of whether a passive neuromuscular training intervention based solely on AFES could be used to improve unassisted respiratory function in tetraplegia.

Prior research had also demonstrated the efficacy of AFES as a respiratory neuroprosthesis [24, 57–59, 78, 85, 87, 104, 132–134, 140]. The majority of these previous studies used a cross-sectional design in which measurements were collected on a single day of assessment. Salmons and Jarvis [124] suggested that using an AFES respiratory neuroprosthesis for a period of time may result in changes in contractile properties of the abdominal muscles, which could affect the efficacy of AFES to enhance unassisted respiratory function. However, only one study, which was published after the conclusion of the clinical work in this thesis, has investigated this issue [104].

From the ideas of using AFES for respiratory neuromuscular training and of using AFES as a respiratory neuroprosthesis, the question of clinical application arises. Previous work has shown that an improvement in respiratory outcome

measures is associated with a reduction in respiratory complications in tetraplegic patients [27]. In addition, it has been shown that an AFES respiratory neuro-prosthesis can be used to support periods of unassisted breathing in tetraplegic patients who are unable to breathe spontaneously [78]. These findings provide the foundation for using AFES as a tool to wean patients from MV. Prolonged MV has considerable health implications for patients [152], and therefore this previously unexplored application of AFES warrants investigation.

Central to the clinical adoption of AFES is the technology used to support the applications. Gollee et al. previously designed an AFES control system that applied AFES automatically in synchrony with a patients volitional exhalation [57]. The system required that patients wear a spirometer connected to a face mask, which is not practical solution. Therefore, subsequent studies demonstrated the feasibility of using alternative respiratory sensors [55,60]. A quantitative analysis on the accuracy of an automatic stimulation system using alternative sensors had not been performed.

Based on the open questions presented above, this thesis had four aims:

1. To determine the effect of a AFES training on unassisted respiratory function in tetraplegia (i.e. using AFES for neuromuscular training).

2. To determine the effect of using AFES training on AFES-assisted respiratory parameters (i.e. the effect of AFES training on an AFES prosthesis).

3. To determine the feasibility of using AFES to assist with weaning tetraplegic patients from MV.

4. To design and determine the performance of an automatic AFES system using a non-invasive respiratory sensor.

9.1 AFES for Respiratory Neuromuscular Training

The main findings of this thesis when using AFES for respiratory neuromuscular training were:

- Unassisted FVC improved significantly over three weeks of passive AFES neuromuscular training and this improvement was sustained three weeks after the cessation of training (Chapter 4). In addition, four weeks of AFES neuromuscular training was correlated with an increase in unassisted FVC in a tetraplegic patient who was weaning from MV (Chapter 7).

- Unassisted CPF improved significantly and PEF tended to improve over three weeks of passive AFES neuromuscular training (Chapters 4 and 5).

9.1.1   Physiological Mechanisms

The abdominal muscles were paralysed in the tetraplegic patients included in this thesis and therefore it is unlikely that an increase in abdominal muscle strength would have affected unassisted forced exhalation. FVC, PEF, and CPF are expiratory manoeuvres that depend on expiratory muscle strength but also on inspiratory capacity. This is evidenced by the fact that FVC and PEF are greater when measured from total lung capacity rather than FRC [159], and by the results of this thesis which showed (i) a significant relationship between CPF and V_I (Chapter 5) and (ii) that the increase in CPF over the training period correlated with an increase in V_I. There are at least four possible explanations for an increase in inhalation capacity following AFES neuromuscular training:

1. AFES training improved the fulcrum effect of the diaphragm contracting against the abdominal contents.

2. AFES affected the diaphragm either by unintended stimulation of the phrenic nerve, or by moving the muscle through an increased range of motion compared with unassisted breathing.

3. AFES breathing increased the compliance of the lung making it easier for the lung to expand.

4. AFES training enhanced the patient's ability to coordinate their breathing muscles.[1]

   Given the patient population investigated in this study, and previous authors' findings that unassisted respiratory function can improve markedly during the first year of a tetraplegic SCI [86,115], it is possible that some of the improvement in unassisted outcome measures over the training period can be attributed to natural recovery[2]. It seems unlikely that this is the only explanation for two reasons:

1. The results of the main clinical study of this thesis (Chapters 3 to 6) showed that (i) during the control period (A1 to A2) there was either no change

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[1]These mechanisms are explained in full in the discussions presented in Chapters 4 and 7

[2]Where natural recovery in this case was defined as the recovery that would have occurred even if the patients had not participated in the AFES training intervention

(for FVC and PEF) or a reduction (for CPF) in the unassisted outcome measures, and (ii) during the follow up period (between A5 and A6) there was either a small change relative to the change during the training period (for FVC), or a reduction (for PEF and CPF) in the unassisted outcome measures.

2. In the MV case study presented in Chapter 7 there was a substantial improvement in FVC during four weeks of AFES neuromuscular training that followed eight weeks of conventional care, in which FVC changed only modestly.

Although the design of the studies and the outcomes of the statistical analysis in this thesis do not allow firm conclusions to be drawn, the aggregation of these observations demonstrate the feasibility of the AFES neuromuscular training approach and provide a framework for a follow up controlled trial.

9.1.2 Comparison with Other Forms of Respiratory Muscle Training

The work in this thesis was the first to investigate a passive AFES neuromuscular training programme. Respiratory muscle training can be divided into active or passive training programmes based on whether they require patient interaction. Other passive respiratory muscle training programs have included: neuromuscular training of the abdominal and pectoral muscles [27]; and FMS based neuromuscular training of the abdominal muscles [90]. Other active respiratory muscle training programs have included breathing exercises complemented with AFES [159]; AFES-assisted coughing [104]; and respiratory muscle training using a flow resistant mouthpiece [13].

The increase in unassisted FVC, PEF, and CPF through the training programme investigated in this thesis was comparable to the results of two previous studies that included AFES [104, 159] but smaller than in other previous studies that incorporated AFES [27, 87], and that used other forms of respiratory muscle training [13]. Other respiratory muscle training programs have resulted in significant increases in unassisted MEP [13, 27], which was not found in the present study. A major difference between the current study and other respiratory muscle training studies is the duration of the training programme, which was shorter in the current study. Given this methodological difference and that there was no evidence in the current study to suggest that FVC, PEF and CPF would not have improved further if the training period was increased (perhaps to the extent of

producing a significant result for PEF), the author believes it would be premature to draw conclusions on the most effective training modality.

Practically, the AFES neuromuscular training programme presented in this thesis was straightforward to implement and was easily incorporated within the patient's existing rehabilitation timetable. The author believes that AFES neuromuscular training has a practical advantage over other training modalities for two reasons. Firstly, unlike abdominal and pectoral neuromuscular training [27], electrodes need only to be applied to one muscle group. Secondly, it is passive, which allows patients to complete other activities at the same time as AFES neuromuscular training. This was demonstrated in the main clinical study of this thesis by the three patients who completed their training sessions while undergoing hand therapy.

9.1.3 Technological Implementation of AFES During Training

The abdominal muscles are a major muscle of expiration and can increase the work of breathing if they contract during inhalation. Therefore, it is important to synchronize AFES with a patient's volitional breathing pattern. In the AFES training protocol used in this thesis, basic open-loop control was used to approximately apply stimulation in phase with a patient's volitional exhalation. There were two limitations to this approach. Firstly, stimulation had to be synchronized manually with the patient's voluntary exhalation, both at the start, and periodically throughout the training session. Secondly, stimulation was not always delivered at the same time relative to exhalation.

As part of this thesis two new automatic stimulation trigger systems were designed. The first system used a nasal thermocouple as the respiratory sensor and the second system incorporated a piezoelectric belt worn around the chest of the user. It was concluded that the first system was most suitable for mobile patients and the second system was most suitable for patients on MV. It was demonstrated that both of the systems achieved high sensitivity and a low error rate during varying breathing patterns. Either of these systems could be integrated with a FES stimulator to allow AFES muscle training to be consistently and simply applied in a wide range of settings.

9.2 AFES as a Respiratory Neuroprosthesis

The main findings of this thesis on the application of AFES as a neuroprosthesis were:

1. AFES-assisted pulmonary function measures (FVC, FEV_1, PEF, and MEP) were significantly greater than unassisted pulmonary function measures (Chapter 4).

2. AFES-assisted CPF was not significantly greater than unassisted CPF (Chapter 5).

3. AFES-assisted V_T and $\dot{V}$ were significantly greater than unassisted V_T and $\dot{V}$. In addition, there was a significant reduction in ET_{CO_2} during AFES-assisted breathing in those patients who had the greatest AFES-assisted V_T (Chapter 6 and 7).

4. AFES-assisted FVC improved significantly, and AFES-assisted FEV_1, PEF and CPF tended to improve over three weeks of AFES training. Quiet breathing ventilatory parameters did not change over the course of the training period (Chapter 4 to 6).

5. The difference between the AFES-assisted and unassisted outcome measures studied did not change over three weeks of abdominal muscle training (Chapters 4 to 6).

9.2.1 Physiological Mechanisms

Acute Effects

The results of this thesis were consistent in demonstrating that AFES-assistance augments unassisted breathing volumes. This finding can be explained by the same mechanism of action that describes the effect of a normal physiological contraction of the abdominal muscles during breathing. When the abdominal muscles contract during exhalation, the abdominal viscera are pushed upward and cause the lungs to empty past FRC. This movement augments expiratory volume, whereas the subsequent passive recoil of the lung back to FRC augments inhalation [150].

During quiet breathing, the results of this thesis showed that the increase in V_T was not associated with an increase in ET_{CO_2} (which is used as a measurement of blood homeostasis and metabolic demands) in any of the subjects whose

AFES-assisted V_T was greater than unassisted V_T (defined as responder subjects). In fact, for the patients who displayed the largest AFES-assisted V_T, a sharp decrease in ET_{CO_2} was observed. This suggests, as discussed in Chapter 6, that the difference between unassisted and AFES-assisted V_T was at least sufficient to offset the additional metabolic demands of the contracting abdominal muscles. In addition, during AFES supported weaning sessions, an increase in blood oxygenation was observed (Chapter 7). The corroboration of these findings suggest that AFES-assisted breathing is metabolically efficient.

In this thesis it was shown that AFES had an inconsistent effect on peak expiratory flow rates. During standardized clinical testing, AFES-assisted PEF was greater than unassisted PEF (Chapter 4). In contrast, a difference between unassisted CPF and AFES-assisted CPF was not found (Chapter 5). Since both of these findings were associated with the same group of subjects, differences in the measurement protocol offer the most likely explanation for these apparently contradictory results. In this regard there were three important differences.

Firstly, the inhalation volume that preceded the expiratory manoeuvre was greater in the measurement of PEF when compared with the measurement of CPF. As discussed in previous chapters, the expiratory elastic recoil of the lung increases in proportion to the inhalation volume. In addition, the results presented in Chapter 5 showed a significant linear relationship between inhaled volume and CPF. Therefore, it may be that AFES-assisted cough is only effective following a large inhalation.

Secondly, the timing of stimulation in relation to the respiratory cycle differed between the two tests. In the measurement of AFES-assisted PEF, stimulation was applied at the onset of exhalation. In comparison, during the measurement of CPF stimulation was applied just before the start of exhalation, during the glottal closure phase. Applying stimulation at the end of inhalation may have been distracting for the patient, possibly interfering with their respiratory muscle co-ordination.

Thirdly, the underlying physiology that is described by PEF and CPF is different. PEF is dependent on the *instantaneous* increase in intrathoracic pressure that results from expiratory muscle contraction. In comparison CPF is dependent on the *build up* of pressure that is generated during the glottal closure phase of the cough.

Chronic Effects

Although the main clinical study conducted in this thesis showed improvements in AFES-assisted outcome measures through the training programme, the difference between the AFES-assisted outcome measures and the unassisted outcome measures did not change. These results suggest that the improvement in AFES-assisted outcome measures were as a result of the improvement in unassisted outcome measures rather than a consequence of an improvement in abdominal muscle contractile properties. One explanation is that the abdominal muscles in tetraplegia cannot be trained effectively. Although this seems unlikely as there have been several previous studies that have shown changes in the properties of other muscles following FES training [11, 131], McBain et al. [104] did not find a change in abdominal muscle strength following six weeks of AFES-assisted cough training. Other possible explanations are:

1. Three weeks of AFES training are insufficient to induce a change in the properties of the muscle. This is supported by previous research which has shown that the at least four weeks of electrical muscle stimulation training is required before morphological change occurs in the muscle [96].

2. AFES caused an unmeasured effect on the properties of the abdominal muscles. The outcome measures included in this thesis were mostly dependent on the power, rather than the fatigue resistance, of the abdominal muscles. It is plausible that the AFES training programme improved the fatigue resistance but not the strength of those muscles.

The current knowledge of the effect of abdominal muscle training on AFES-assisted cough is incomplete and further studies are required with a focus on the underlying mechanisms. This should help to determine the potential of AFES training to improve AFES-assisted cough and allow future paradigms to be optimised for this application.

9.2.2 Comparison with Other Respiratory Neuroprosthesis

Previously, it had been shown that AFES assistance can augment unassisted respiratory outcomes measured during quiet breathing, FVC and MEP tests [57–59,78,85,132,134]. The results presented in this thesis corroborate this conclusion.

Contrary to the results presented in this thesis, previous studies have shown that AFES-assisted CPF is greater than unassisted CPF [24, 87, 104, 140]. A

number of possible explanations for this contradiction are presented in Chapter 5. However, the results presented in this thesis are unique in that both CPF and PEF measurements were made on the same subjects. Therefore, as discussed above, the measurement and stimulation protocol used in this thesis offer the most likely explanations for these contradictory results.

Previous research on other types of respiratory neuroprosthesis has mainly concentrated on restoration of cough in tetraplegia. For this application, AFES, FMS [91] and SCS [40,41] have all been investigated. Of the three approaches SCS has been shown to provide the greatest improvement compared with unassisted CPF. However, since SCS has practical disadvantages it was reasoned that AFES-assisted cough could be useful if it could provide a clinically significant cough (defined as CPF greater than 4.5 L/s [146]). Although this thesis did not find a difference between unassisted and AFES-assisted CPF at baseline, it was found that AFES-assisted CPF increased by 0.38 L (11%) over the training programme. A similar result was shown by Mcbain et al. [104]. These findings, combined with the research of Butler et al., which demonstrated a mean AFES-assisted CPF of 4 L/s [24], suggests that, while SCS is the most effective method to augment cough, AFES-assisted cough has the potential to become clinically useful in tetraplegia.

9.2.3 Technological Implementation of an AFES Respiratory Prosthesis

Patients with tetraplegia have limited means to interact with their environment. This has two implications for a respiratory neuroprosthesis. Firstly, the system would most likely be applied to the patient by a caregiver. Therefore, it should be designed in such a way that it can be worn throughout the day and could be operated by the patient when needed. Otherwise, the device would reduce rather than enhance patient independence. Secondly, the device should require minimal user interaction.

Previous studies, which have automatically synchronised AFES with a patient's volitional breathing pattern, have either used a spirometer or electromyography measurements of the pectoral muscles. A spirometer measures airflow rate from the mouth, and thus is not a practical sensor for a neuroprosthesis as it interferes with other activities such as eating or speaking. Pectoral electromyography measurements can only be used to trigger stimulation for coughing and not quiet breathing. The results of this thesis demonstrated that a non-invasive sensor, such as a plethysmographic belt or a nasal thermocouple, can be used

to replace the spirometer in an automatic stimulation system for quiet breathing. Using these non-invasive sensors allow for a practical AFES system to be developed. The components of this system (the sensor technology, stimulation electrodes and stimulator) could be incorporated into a garment that would be worn under a patient's normal clothes. Such a system could be put onto the patient in the morning and taken off at night by the caregiver, allowing the patient to use the device when necessary.

There is a paucity of research on user-friendly methods to control AFES. The most comprehensive control scheme to date was proposed by Gollee et al. [57]. This control scheme monitored the patient's respiratory pattern and modified stimulation output accordingly. An adaption of this system was used in the main clinical trial of this thesis. Although the system worked well for some patients, it was inaccurate at triggering stimulation for other subjects. Accuracy could be poor during cough for those subjects whose peak inspiratory flow was approximately equal during cough and quiet breathing. In addition, the accuracy of the quiet breathing cross-correlation trigger was not robust to changes in breathing pattern, which for some patients varied considerably, either within a single assessment session or between assessment sessions. Recent research on this topic is investigating statistical classification methods [105] to improve upon the control schemes proposed by Gollee et al [57]. However, this approach is yet to be throughly tested in a wide tetraplegic population. Although this approach is worthwhile and promising, it is the authors opinion that simpler control methods should also be considered.

For a system to assist with breathing volume in tetraplegia, the automatic triggering scheme proposed in Chapter 8 could be combined with a simple on and off switch. This would not be difficult to implement as many tetraplegic patients currently use simple buttons to control other devices which they use. Furthermore, it is more likely to be accurate as the algorithm relies only on the onset of exhalation to trigger stimulation, rather than the shape of the breath as used in the system by Gollee et al. [57].

For a cough stimulation system, a simple approach of having the patient control the timing of the stimulation manually is recommended for two reasons:

1. It would remove the problem of detecting a cough accurately. This is not a trivial task, especially in an online system. This is highlighted by the fact that, despite several attempts by different groups, there is not an accurate cough monitor [114].

2. In the studies that have been most effective at improving cough using AFES,

stimulation has been triggered manually, either by the researcher or the patient. Furthermore, Butler et al. [24] have shown that there is no difference between cough stimulation initiated by the patient and cough stimulation initiated by a second person.

9.3 Clinical Implications

Despite improvements in respiratory health care over the last 20 years, respiratory complications remain one of the leading causes of death and morbidity for patients with tetraplegia [25].

9.3.1 Coughing in Tetraplegia

A major contributor in the development of respiratory complications in tetraplegia is the lost ability to cough. Although, SCS-assisted CPF [41] is greater than AFES-assisted CPF [24], both methods have the potential to provide a clinically useful cough. Therefore, it is important to consider the practical aspects of both technologies. A cough respiratory neuroprosthesis should, ideally, be available to patients at all times. In this respect, a SCS system could be regarded as more practical as it is implanted. On the other hand, a surface stimulation system could be practical if it was incorporated into a garment that could be worn throughout the day. Furthermore, surface stimulation systems are less expensive than implanted systems and do not carry a risk of infection. Therefore, while AFES-assisted cough is not as effective as SCS-assisted cough, there are practical advantages which may make the technology more suited to a different group of patients than would be considered for SCS; for example those patients who have a borderline clinically effective cough. For this reason an AFES based cough neuroprosthesis remains a clinically useful possibility and should be researched more thoroughly.

9.3.2 Dyspnea and Respiratory Failure

Although not as common as respiratory infection, dyspnea [23] and acute respiratory failure [154] remain a problem in tetraplegic patients. Previously, authors have shown that AFES can be used to augment unassisted V_T in patients [57,59,134]. The results presented in this thesis have added to this finding by demonstrating that this effect can be observed across a wide demographic of patients. In addition, the results in this thesis suggest that AFES-assisted

breathing is metabolically efficient. This has important clinical implications as it suggests that AFES-assisted breathing could be useful during times of respiratory stress, e.g. a patient suffering from dyspnea secondary to respiratory infection. As with an ideal cough AFES neuroprosthesis, it would be desirable to incorporate the stimulation system into a practical form so that it could be easily adopted into the clinic.

9.3.3 AFES to Assist Weaning from Mechanical Ventilation

Chapter 7 presented the first study which demonstrated the use of AFES as an intervention to assist in the process of weaning patients from MV. This application is particularly interesting in the context of this discussion, not only because of its clinical implications, which are discussed fully in Chapter 7, but because it utilises AFES both as a neuromuscular training device and as a respiratory neuroprosthesis.

AFES was most useful as a respiratory neuroprosthesis at the start of the weaning process, when the patient was only able to sustain three minute periods of volitional breathing. By augmenting the patients unassisted V_T, AFES allowed the patient to breathe for extended periods without ventilator support. Although it was not demonstrated in this thesis, it is reasonable to assume that this allowed the weaning process to begin sooner than otherwise possible. This may have been beneficial for the patient not only physiologically but perhaps also psychologically. The initial sessions of ventilator free breathing can be extremely stressful for a patient: AFES-assisted breathing may offer a compromise between ventilator supported breathing and unassisted breathing.

AFES was used as a neuromuscular training device in the later stages of weaning, when the second AFES intervention was initiated and the patient was able to breathe volitionally for 10 hours per day. Although only a single patient, the correlation between the start of the AFES intervention and the immediate improvement in daily ventilator free breathing was striking. Furthermore, this observation was congruent with the discussion presented in Section 9.1, which concludes that AFES neuromuscular training improves breathing capacity in patients in tetraplegia.

9.4 Commerical Aspects

There are several commercially available stimulators that are currently available for:

1. The general application of FES (for example, Empi Continuum [1]). These are prescription devices that are capable of producing the levels of stimulation output used in the studies in this thesis. The intended uses of these stimulators includes reducing muscle atrophy and improving range of motion.

2. Toning the abdominal muscles (for example, Slendertone Flex [3]). These are over the counter devices that are capable of limited stimulation output. The intended use of these stimulators is to improve abdominal muscle tone in healthy adults.

3. Correction of dropped foot in SCI (for example, Odstock ODFS Pace [2]). These are prescription FES stimulators and produce are capable of producing the levels of stimulation output used in the studies in this thesis.

There are currently no commercially available stimulators that provide electrical stimulation to the abdominal muscles in synchrony with exhalation. Stimulation technology and its risks are well understood. Furthermore, the results of this thesis (Chapter 8) established that triggering stimulation with a user friendly respiratory sensor is feasible. Therefore, from a technical perspective it would be relatively straightforward to develop a commercially viable device. The results of this thesis have also provided the clinical justification to conduct a larger scale clinical trial, the results of which would be needed to obtain regulatory clearance for the device and to justify payment for the device by the health care payer (e.g. the National Health Service in the United Kingdom).

9.5 Thesis limitations

Individual chapters cover the study limitations specific to that chapter. In this section, the most important study limitations as they relate to conclusions drawn from this thesis will be reiterated.

One of the main clinical contributions of this thesis, was the investigation of AFES training on unassisted and AFES-assisted respiratory outcome measures. Several reviewers, from the publication of the data presented in Chapter 4, commented that the most important limitation in this investigation was the choice

of study design. The choice of a longitudinal design as opposed to a randomised controlled trial was made for several reasons.

This was the first investigation of a passive AFES training program on respiratory function measures. Therefore, information on the variability of the proposed outcome measures, which is needed for a randomised controlled trial power calculation, was not available.

Secondly, since there is a high level of inter-subject variability in the tetraplegic population, especially those who are in the sub-acute phase of recovery, which included the majority of patients studied in this thesis, it was considered that the scale of an appropriately powered randomised controlled trial, would not be justified at such an early stage of this research. Nonetheless, the lack of a matched control group limits the strength of the conclusions that can be drawn from this work.

In retrospect, the design of the main clinical trial in this study could have been improved in several ways.

1. The pre-training control phase should have been increased to match the duration of the training and follow up phase. As observed in this thesis, there was considerable intra-subject variability during successive weeks of measurement. Had the control phase duration been increased, a stable estimation of the pre-training temporal change in respiratory function could have been estimated. This could have been compared directly to the change in respiratory function over the training period and would have greatly improved the strength of the conclusions drawn.

2. The length of the training intervention should have continued for longer than three weeks. Research has shown that it takes at least four weeks of FES training before morphological change is observed in the muscle.

3. A measurement of muscle fatigue should have been included in the main clinical study since the training scheme used may have had an unobserved effect on the fatigue resistance of the abdominal muscles to repeated contraction by AFES

The main limitation from the case study on weaning from MV was that only one subject was included. Therefore, while the results demonstrate the feasibility of the approach proposed, they have to be taken as preliminary.

Finally, in the last experimental chapter, in which an automatic stimulation system was developed, the main limitation was that the study was completed using healthy volunteers and not tetraplegic patients. Since tetraplegia is known

to affect the mechanics of breathing, the results presented need to be verified in this patient population.

9.6 Conclusions

1. The use of AFES to improve respiratory function in tetraplegia can be split into two paradigms: as a neuromuscular training tool and as a respiratory neuroprosthesis.

2. Passive AFES neuromuscular training is a feasible method of improving unassisted respiratory function in tetraplegia. Furthermore, it has several practical advantages over other types of respiratory muscle training. The mechanism underlying the changes in unassisted respiratory function observed is currently not fully understood but several hypothesis were generated in this thesis. An investigation of these mechanisms may maximise the benefit of AFES neuromuscular training in tetraplegia. Collectively, the results presented in this thesis provide the basis for a future controlled trial of the technique.

3. An AFES neuroprosthesis can be used to improve ventilation during quiet breathing in tetraplegia. Moreover, the results of this thesis suggest that the technique is metabolically efficient.

4. Using AFES is a feasible method to assist in the process of weaning a patient from MV. In this application, AFES was shown to be useful as both a neuroprosthesis, to allow the weaning process to begin earlier than would otherwise be possible, and for neuromuscular training, to improve unassisted respiratory function. The combination of these effects may improve the probability of weaning and reduce the time to complete liberation from MV. Although only a single case study, these results provide the basis for a future path of exciting research.

5. AFES can be synchronised automatically with a patient's volitional exhalation by a system that uses either a thermocouple or a piezoelectric belt that encircles the chest. This finding should be utilised in the future development of a practical AFES system that can be used both for spontaneously breathing tetraplegic patients and as a tool to aid the process of weaning from mechanical ventilation.

6. Collectively the results presented could also be used as the first step in the development of a commercially viable device.

To conclude, the work of this thesis has delineated several possible applications of AFES for the improvement of respiratory function in tetraplegia. Furthermore, contributions to the body of evidence to support these applications have been made and possible explanatory mechanisms have been provided. Lastly, advances in the technology to support the practical implementation of these applications have been made. Although the conclusions that have been drawn here should be taken as preliminary, they provide exciting possibilities for future research, which could ultimately be a great boon to the health of patients with tetraplegia.

Chapter 10

Future work

In the authors opinion, using AFES for neuromuscular training in spontaneously breathing tetraplegics and as a tool for ventilator weaning are the most promising areas for future work. Therefore this chapter will present future work related to these applications.

10.1 Basic Science

10.1.1 Mechanisms of Action

This thesis proposed four mechanisms of action to explain the effect of AFES neuromuscular training on unassisted breathing capacity in patients with tetraplegia. These mechanisms were:

1. The fulcrum effect.

2. Improvement in diaphragm strength.

3. Increased compliance of the lung.

4. Improved co-ordination of the breathing muscles.

Investigation of these mechanisms is important as it would help to determine the most effective training paradigm.

To determine whether the fulcrum effect is a mechanism associated with AFES training would require the measurement of abdominal muscle tone and abdominal muscle bulk. The former is hard to measure as, currently, there are no currently established methods. One possibility would be to measure the transient gastric pressure during inhalation. If tonus was present in the abdominal muscles, gastric pressure should increase as the abdominal muscles resisted pressure applied to

the intra-abdominal space by the contracting diaphragm. Abdominal muscle bulk could easily be measured using ultrasound similar to the method used by Estenne et al. [51]. An increase in abdominal bulk or gastric pressure from pre to post training would provide indirect evidence of the fulcrum effect. If this mechanism was found to be a real response to AFES training it would suggest that future training paradigms should be designed with the aim of improving abdominal muscle bulk.

Stimulation of the diaphragm may occur from AFES through two pathways: unintentional stimulation of the phrenic nerve and passive stretch of the diaphragm. Unintentional stimulation of the phrenic nerve would result in action potential being sent in both the direction of the diaphragm and the direction of the cervical nerves. Therefore a phrenic electroneurogram [73] could be used to determine whether abdominal stimulation resulted in unintentional stimulation of the diaphragm. This technique is invasive and to the authors knowledge has not previously been used in humans, however, and this experiment would likely have to be completed in an animal model, such as a spinalised dog or cat [44].

It would also be difficult to measure whether a passive stretch of the diaphragm results in muscle fibre activation. Electromyography would not be useful since afferent pathway activity is not an indicator of active efferent pathways. Although it is possible to measure the diaphragm directly using electromyography electrodes placed on a oesophageal balloon this technique would be unable to distinguish between the electrical activity from the diaphragm and the electrical activity from stimulation. A possible solution could be to measure diaphragm electromyography while the abdomen was manually compressed. If diaphragm activity was found in this case it would indicate the benefit of the mechanical action of the abdominal contents, which is present during AFES, on diaphragm activity. If passive stretch of the diaphragm did cause muscle activity, future AFES training protocols could utilise this finding by attempting to maximize the vertical displacement of the abdominal contents during stimulation.

Standard techniques could be used for measuring lung compliance [150] and electromyography could be used to measure respiratory muscle coordination [116].

10.1.2 Muscle Fatigue

The recruitment of muscle fibres using FES is much less efficient than the natural recruitment of muscle fibers [97]. Therefore muscle fatigue is a central issue to any FES application. Related to AFES, muscle fatigue is most important when using AFES as a respiratory neuroprosthesis: by minimising abdominal muscle fatigue

the patient could be supported by AFES-assisted breathing for longer periods. In this respect methods to reduce muscle fatigue caused by AFES would be useful for the application of ventilator weaning, particularly at the start of ventilator weaning where the patient may benefit from longer AFES weaning sessions.

There are several possible approaches to the problem of fatigue. Optimising the stimulation waveform parameters (current, pulsewidth and frequency), stimulation timing, and stimulation electrode position may all be useful. Another option, since both stimulation of the rectus abdominis and external oblique muscles are effective at improving breathing volumes when stimulated individually [56], is to alternate the stimulation of different abdominal muscle groups. This strategy is similar to strategies that have been implemented successfully in other FES applications [15].

10.1.3 AFES Training Paradigm

In this thesis, the maximum duration of a single AFES training session was one hour, the stimulation settings were generally set to produce maximum contraction of the abdominal muscles, and the length of the training paradigm was three or four weeks. The design of this paradigm was based partly on the similar training interventions reported in the literature [27,87,159] and partly on practical limitations (for example it was generally not possible to spend more than an hour with a patient per day due to other rehabilitation commitments). However the design of this paradigm may not be optimal.

In determining the optimal stimulation settings and duration of AFES training sessions the end application should be considered. For example, AFES-assisted, compared to unassisted, tidal volume was greater in almost all of the patients studied in this thesis. Therefore, since the power of the abdominal muscles seems to be sufficient in these patients, the goal of training in the application of AFES as a quiet breathing neuroprothesis should be to maximise the fatigue resistance of the abdominal muscles. In contrast to quiet breathing, coughing is a discreet event that requires short powerful bursts of abdominal muscle contraction. Thus, the goal of training in this application should be to maximise abdominal muscle power, even if it comes at the expense of fatigue resistance.

Neuromuscular training with AFES poses new challenges in developing an optimal training paradigm since the underlying mechanisms are currently unknown, and probably do not depend on the contractile properties of the abdominal muscles (see Section 10.1.1). Future work should concentrate on understanding these mechanisms.

10.2 Clinical Development

10.2.1 Neuromuscular Training

In the studies included in this thesis, pulmonary function measures were used as the main outcome measure. However, the ultimate goal of developing an AFES neuromuscular training programme is to improve the respiratory health of tetraplegic patients. Not only would this reduce morbidity, and potentially mortality, for patients but it would also reduce the economic burden on the health care system.

The primary aim of future work should be to establish the best AFES neuromuscular training parameters to improve pulmonary function measures as described at the start of this section. Subsequently, a link between AFES neuromuscular training and funtional health outcome measures (such as dyspnea, respiratory infections and quality of life) and cost of care of patients should be investigated.

10.2.2 Ventilator Weaning

The results of this thesis showed the feasibility, and demonstrated the potential, of using AFES to assist in the process of weaning patients from MV. Although the results were encouraging, they were from a single case study and further work is required to validate the results.

If it is assumed that AFES is effective at improving weaning outcome for patients, then it follows that AFES should be incorporated as early as possible into the process of weaning a patient from MV. In order to demonstrate the effectiveness of this approach it would be necessary to conduct a study in which weaning with AFES is compared with weaning using conventional techniques. However, there is large variability in the probability of weaning and time taken to wean in this patient group. Accordingly, a large group of patients would be required for the trial to be powered sufficiently. To give it some perspective, a study which compared four different weaning techniques in difficult to wean patients, who did not have a SCI, included 130 patients [47]. To conduct a study with that number of patients in an SCI population would take considerable time and resources.

The large variability in weaning success rate and time taken to wean for mechanically ventilated tetraplegic patients could be reduced with a suitable diagnostic. This would allow similar groups of patients to be identified and would

reduce the number of patients required for a clinical trial to be reduced. Diaphragm needle electromyography has been shown to be an accurate predictor of weaning success in tetraplegic patients [28]. In addition, measurement of the vertical excursion of the diaphragm, using M-mode ultrasound, can indicate total weaning time in non-SCI patients who require MV [81]. Further investigation of these techniques in tetraplegic patients may show that they are useful to define cohorts of patients who have similar weaning characteristics.

An alternative approach for future investigation of AFES in ventilator weaning is to focus on patients who have failed to wean using conventional techniques. In the case study in this thesis ventilator free breathing duration increased substantially through the second AFES intervention. This result was particularly striking since the patient had shown no improvement over the previous eight weeks using conventional techniques. This result could be replicated by testing AFES weaning in patient who had failed to wean using conventional techniques. This group would not need a control group to establish feasibility and could be used to set the stage for a larger scale study.

10.3 Technical Development

In order for any FES application to be adopted in the clinic, the technology should be easy to use. In this thesis an automatic stimulation system which did not require an invasive respiratory sensor was developed. This system was only tested in healthy volunteers and therefore the accuracy of the system to synchronise stimulation with a patients volitional exhalation needs to be verified in a tetraplegic population. While automatic timing of stimulation is obviously essential for a practical AFES system, there are additional features that would also be useful to develop.

Firstly, it would be desirable to have a method by which the stimulation intensity is automatically adjusted to account for muscle fatigue. During the experiments carried out in this thesis, it was necessary to increase the stimulation intensity approximately every five to ten minutes. While this task is not time consuming it would require that the clinician attend to the patient at regular intervals. If a reliable and safe method of automatically increasing the stimulation intensity automatically could be developed, this would allow unsupervised AFES sessions to be completed.

The second feature that would be useful to develop is automatic adjustment of

stimulation parameters to account for varying breathing patterns. While the previous chapter made the point that a simple on and off control would be sufficient for most applications, a robust automatic controller would improve the patient's experience while using the device. Current research is aiming to improve upon the system originally proposed by Gollee et al. [57] by using statistical classification methods [105]. While further development is needed in this approach, it could prove a useful addition to future systems.

Appendix A

Stimulation System Simulink Model

This appendix details the complete Simulink diagram and model parameters for the stimulation system, which was described in Chapter 3 and used throughout the experiments of this thesis.

The stimulation system was modified for the experiment described in Chapter 8 to include analog inputs for the additional respiratory sensors and this is the version of the model that is presented in this chapter. It should be noted that there were several features of this model which were not used in the experiments conducted in this thesis (for example, a delay between exhalation detection and the onset of stimulation could be configured for the quiet breathing stimulation mode). Since these features were not used in the experiments they have not been described in the main body of this thesis.

The organisation of this chapter is as follows. The top-level of the Simulink diagram is shown in Figure A.1 and the parameters for the blocks included in this diagram are given in Table A.1. The sub-functions of this level are described in Table A.1, which references the figures that describe each sub-function. This pattern has been repeated for each level of the diagram. Every Simulink block contains several pages of parameters, only the non-default parameters have been described in this Appendix. In addition, most Simulink blocks include a sample time parameter, this was set to 0.02 (s) for all blocks and therefore has also been omitted from the parameter description tables.
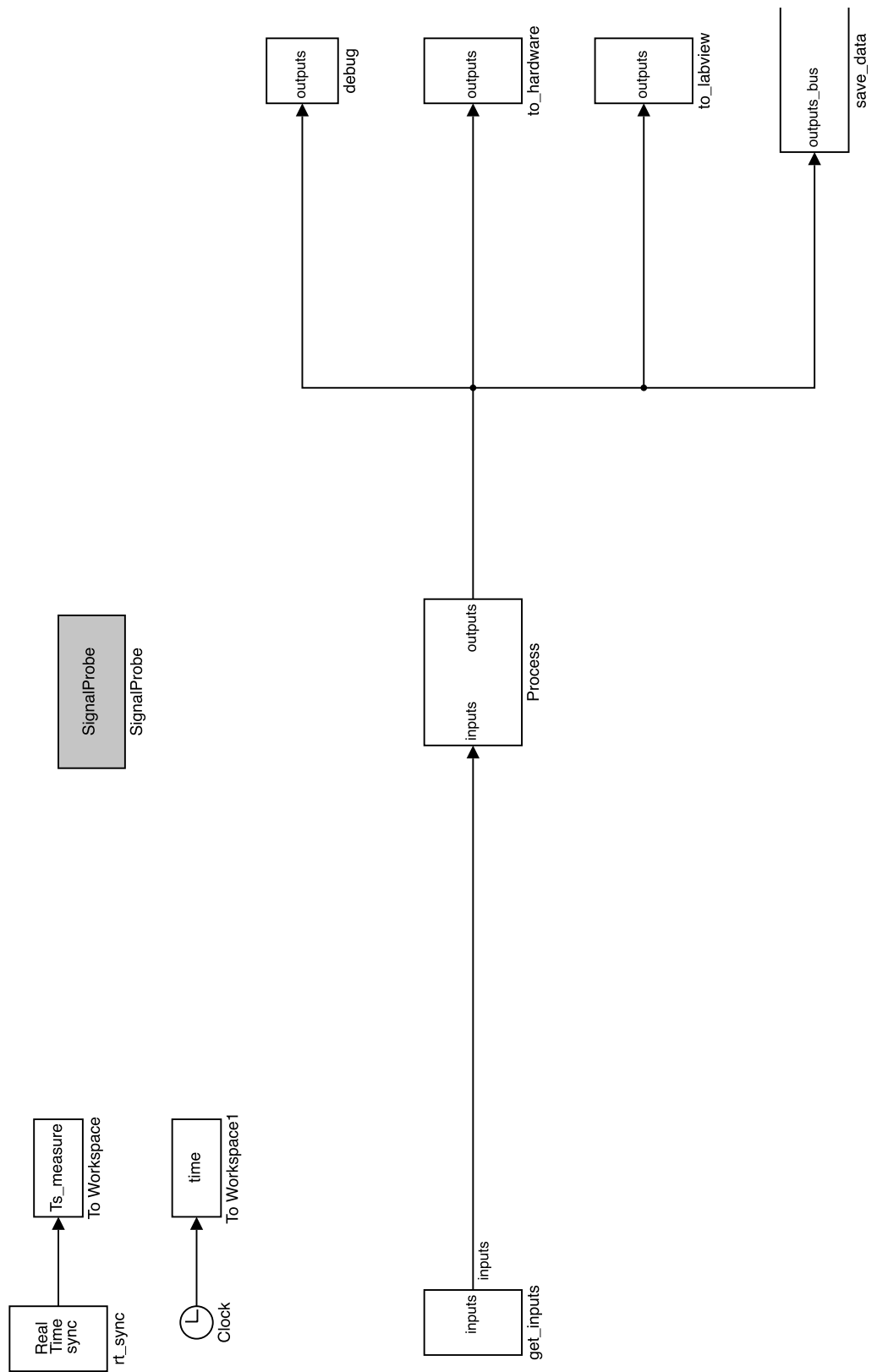
Figure A.1: Assessment.mdl

Table A.1: Block parameters for Assessment.mdl shown in Figure A.1

Name	Type	Parameter	Value	Note
rt_sync	S-function	Ts	0.02	Controlled real-time execution of the model. Written by H. Gollee
To Workspace	To Workspace	Variable name	Ts_measure	
		Save format	Array	
Clock	Clock	-	-	defaults used
To Workspace1	To Workspace	Variable name	Time	
		Save format	Array	
get_inputs	Sub-function	-	-	Figure A.2
Process	Sub-function	-	-	Figure A.9
debug	Sub-function	-	-	Figure A.22
to_hardware	Sub-function	-	-	Figure A.23
to_labview	Sub-function	-	-	Figure A.24
save_data	Sub-function	-	-	Figure A.25
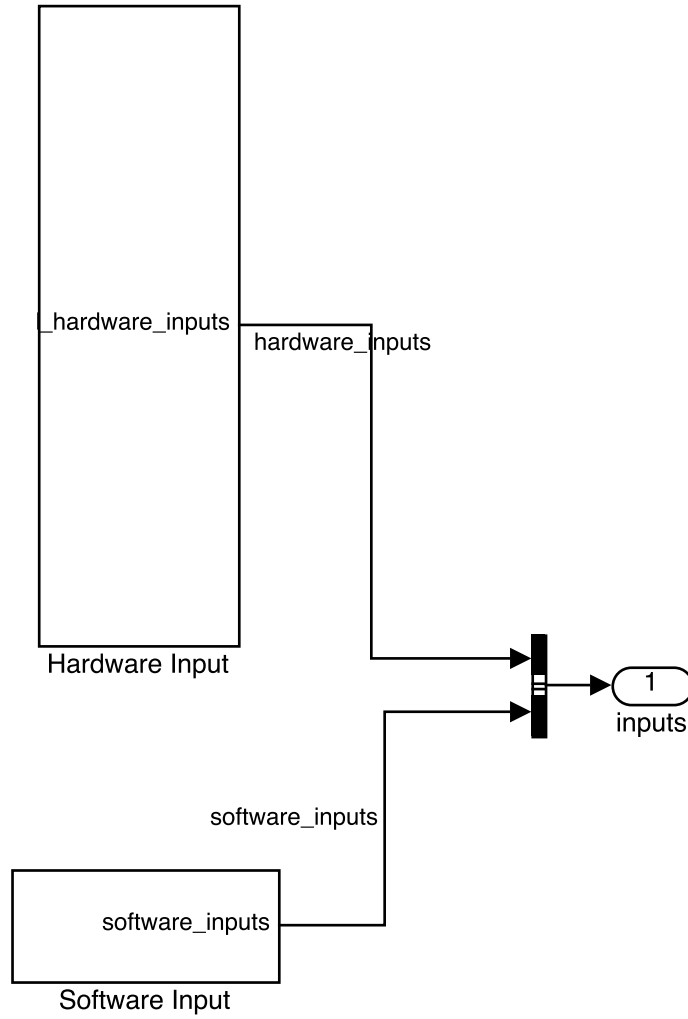
Figure A.2: Assessment/get_inputs.mdl

Table A.2: Block parameters for Assessment/get_inputs.mdl shown in Figure A.2

Name	Type	Parameter	Value	Note
Hardware Input	Sub-function	-	-	Figure A.3
Software Input	Sub-function	-	-	Figure A.5

Figure A.3: Assessment/Hardware Input.mdl

Table A.3: Block parameters for Assessment/get_inputs/Hardware Input.mdl shown in Figure A.3

Name	Type	Parameter	Value	Note
Microloop	Sub-function	-	-	Figure A.3
NI-DAQmx AI	S-function	-	-	Used to read the analog input of the data acquisition card; written by H. Gollee
NI-DAQmx DI	S-function	-	-	Used to read the digital input of the data acquisition card; written by H. Gollee
Logical Operator	Logical Operator	Operator	NOT	
Logical Operator1	Logical Operator	Operator	NOT	
Constant1	Constant	Value	4	
NI-DAQmx DO	S-function	-	-	Used to control digital output of the data acquisition card; written by H. Gollee
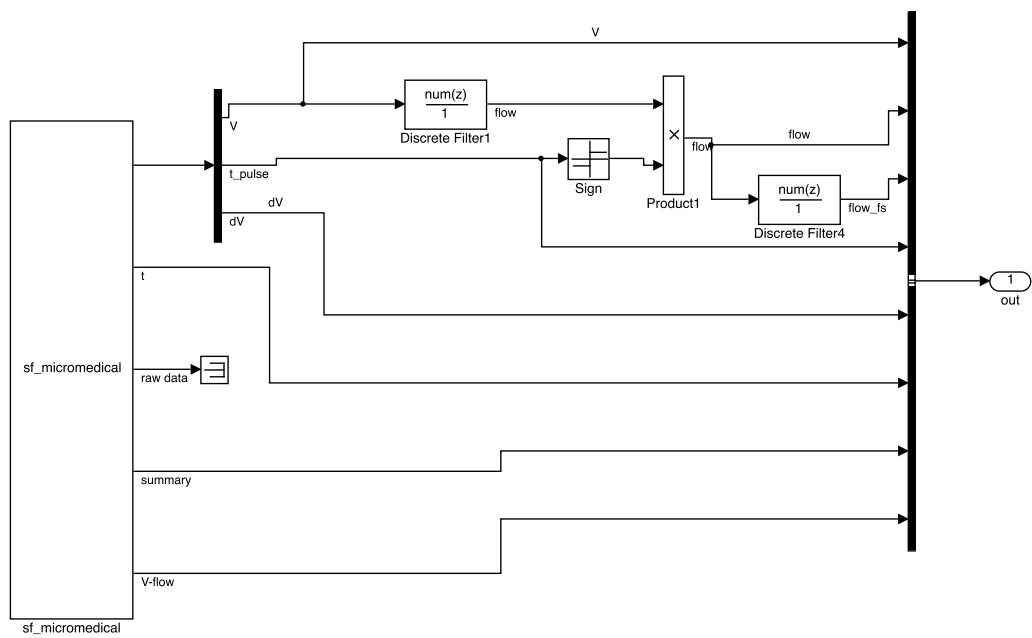
Figure A.4: Assessment/Hardware Input/MicroLoop.mdl

Table A.4: Block parameters for Assessment/get_inputs/Hardware Input/MicroLoop.mdl shown in Figure A.4

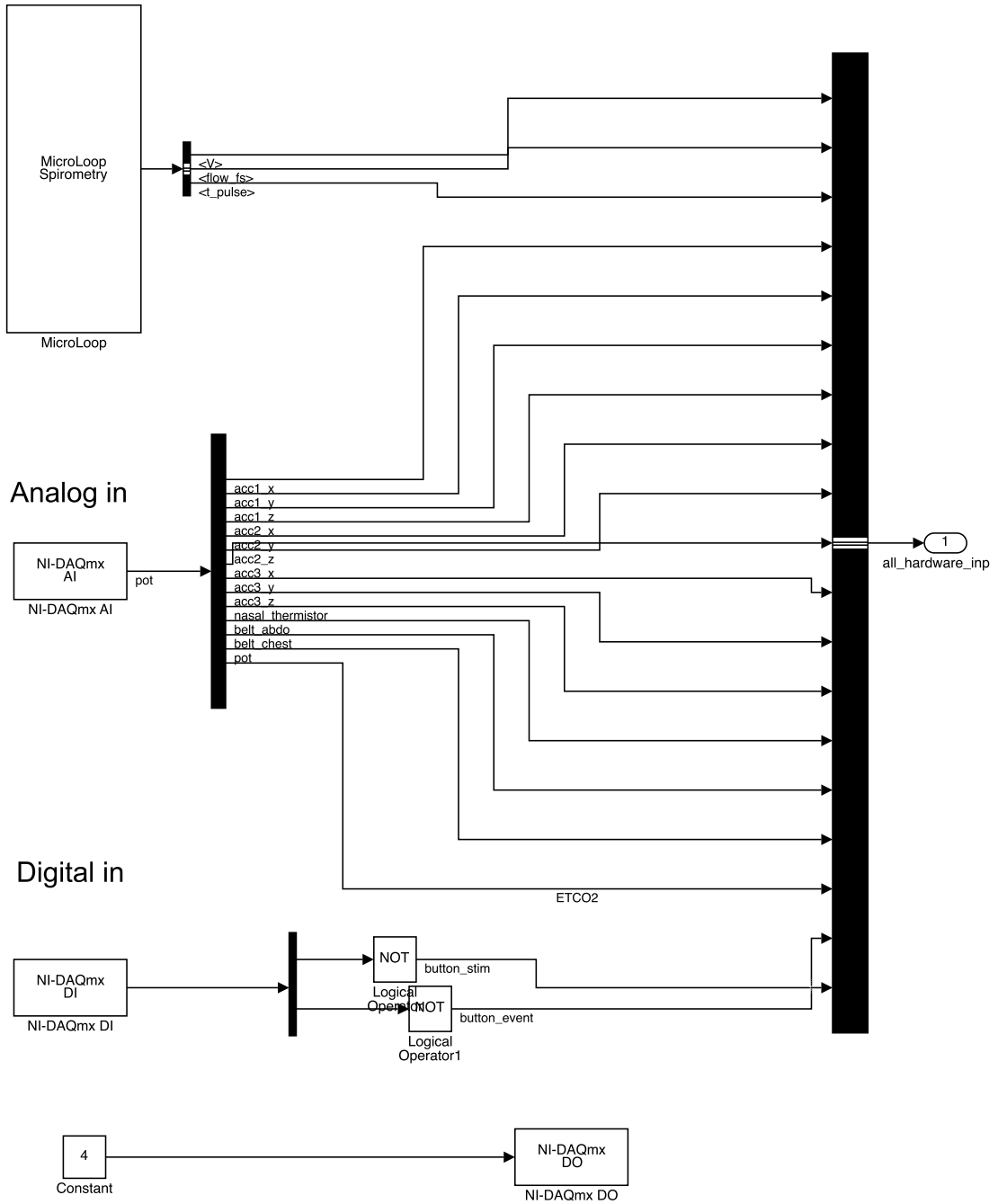| Name	Type	Parameter	Value	Note
sf_micromedical	S-function	-	-	Used to read Spiro_V and Sprio_D from the spirometer; written by H. Gollee
Discrete Filter1	Discrete Filter	Numerator	[1-1]/Ts	Ts is the sample time
		Denominator	1	
Sign	Signum	-	-	Defaults parameters used.
Product1	Product	Number of inputs	2	
Discrete Filter4	Discrete Filter	Numerator	1/N * [ones(1,N)]	N=10
-	-	Denominator	1	
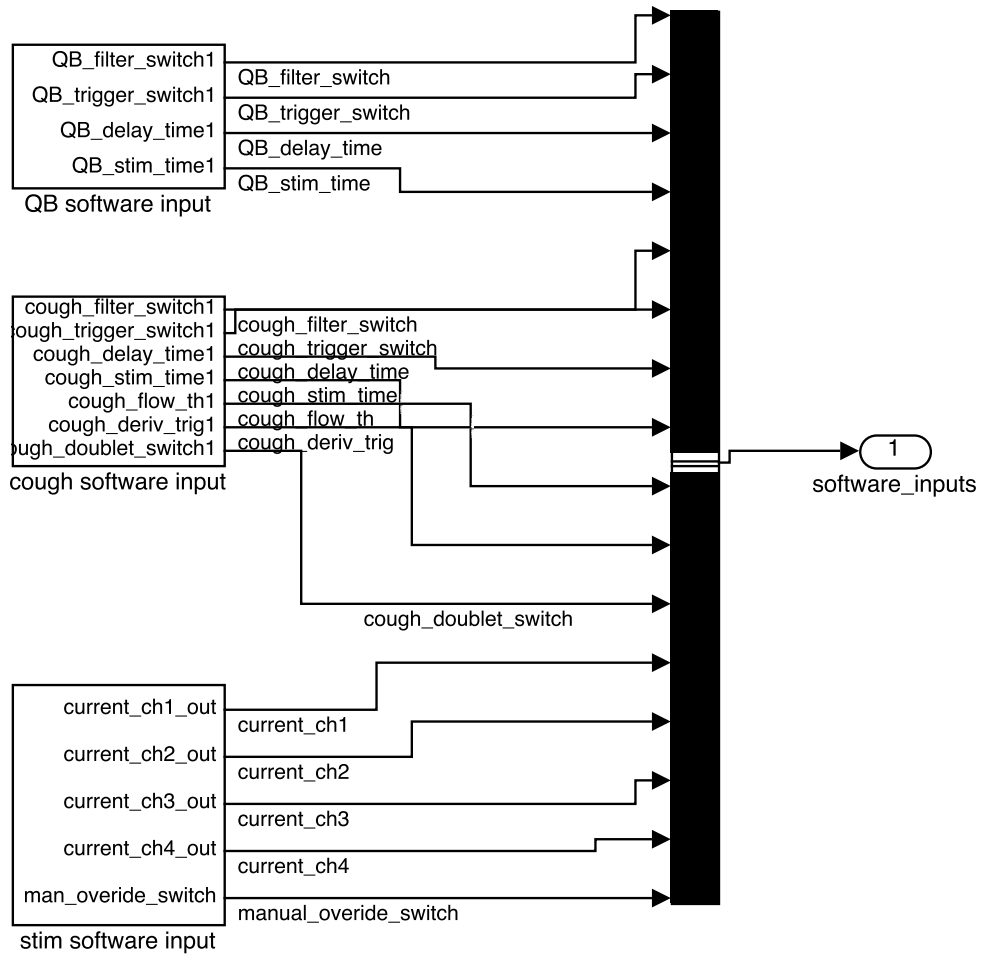
Figure A.5: Assessment/Software Input.mdl

Table A.5: Block parameters for Assessment/get_inputs/Software Input.mdl shown in Figure A.5

Name	Type	Parameter	Value	Note
QB software input	Sub-function	-	-	Figure A.6
cough software input	Sub-function	-	-	Figure A.7
stim software input	Sub-function	-	-	Figure A.8
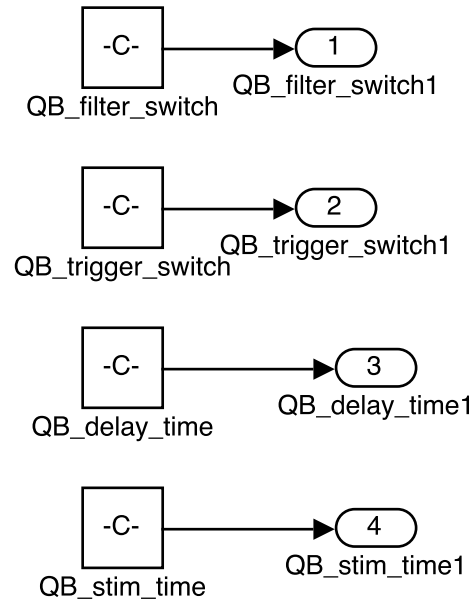
Figure A.6: Assessment/Software Input/QB software input.mdl

Table A.6: Block parameters for Assessment/get_inputs/Software Input/QB software input.mdl shown in Figure A.6. All of the values for these blocks were set by the GUI.

Name	Type	Parameter	Value	Note
QB_filter_switch	Constant	Value	1 or 0	Set to 1 for all subjects
QB_trigger_switch	Constant	Value	1 or 0	
QB_delay_time	Constant	Value	≥ 0	Set to 0 for all subjects
QB_stim_time	Constant	Value	> 0	Set to 1 for all subjects
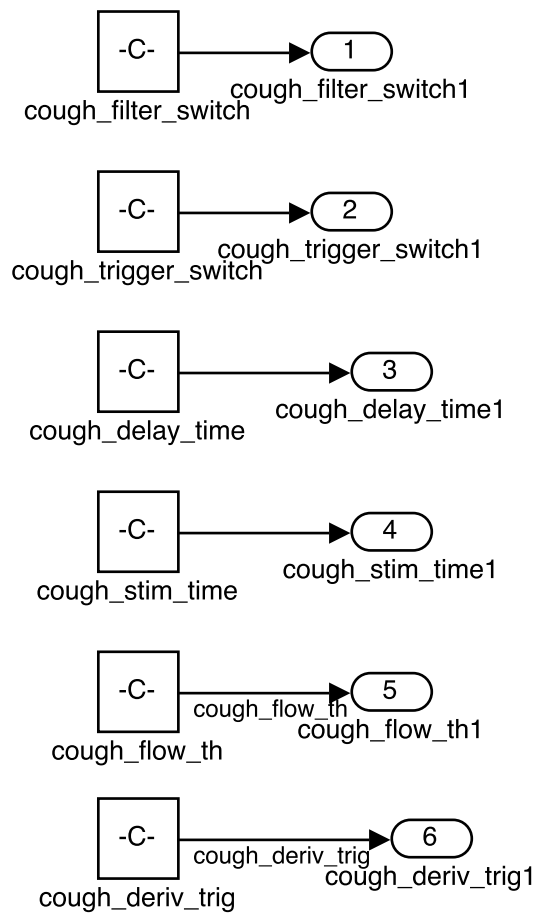
Figure A.7: Assessment/Software Input/cough software input.mdl

Table A.7: Block parameters for Assessment/get_inputs/Software Input/cough software input.mdl shown in Figure A.7. All of the values for these blocks were set by the GUI.

Name	Type	Parameter	Value	Note
cough_filter_switch	Constant	Value	1 or 0	Set to 1 for all subjects
cough_trigger_switch	Constant	Value	1 or 0	
cough_delay_time	Constant	Value	≥ 0	Set to 0 for all subjects
cough_stim_time	Constant	Value	>0	Set to 1 for all subjects
cough_flow_th	Constant	Value	<0	τ_{cflow}
cough_deriv_trig	Constant	Value	>0	τ_{cdflow}
cough_doublet_switch	Constant	Value	1 or 0	

Figure A.8: Assessment/Software Input/stim software input.mdl

Table A.8: Block parameters for Assessment/get_inputs/Software Input/stim software input.mdl shown in Figure A.8. All of the values for these blocks were set by the GUI.
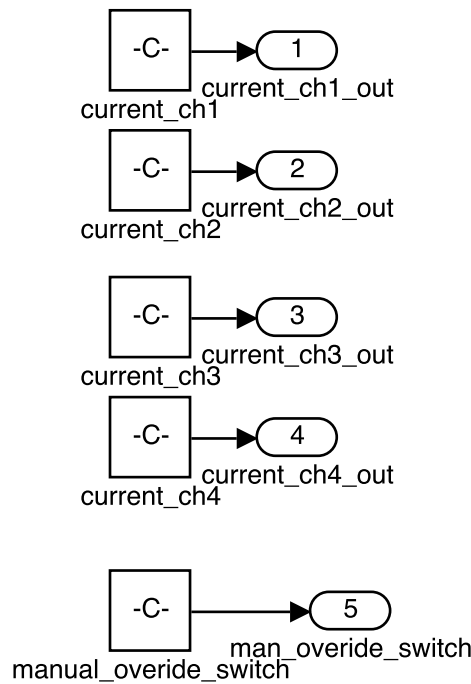
Name	Type	Parameter	Value	Note
current_ch1	Constant	Value	0 - 120	
current_ch2	Constant	Value	0 - 120	
current_ch3	Constant	Value	0 - 120	
current_ch4	Constant	Value	0 - 120	
manual_overide_switch	Constant	Value	0 or 1	

Table A.9: Block parameters for Assessment/Process.mdl shown in Figure A.9.

Name	Type	Parameter	Value	Note
QB_trigger	Sub-function	-	-	Figure A.10
cough_trigger	Sub-function	-	-	Figure A.14
breath_analysis	Sub-function	-	-	Figure A.19
set_stim_param	Sub-function	-	-	Figure A.21
const	Constant	Value	1	
man_override	Switch	Criteria	u2 > Threshold	
		Threshold	0.5	
MinMax	MinMax	Function	max	
Product1	Product	-	-	Defaults used
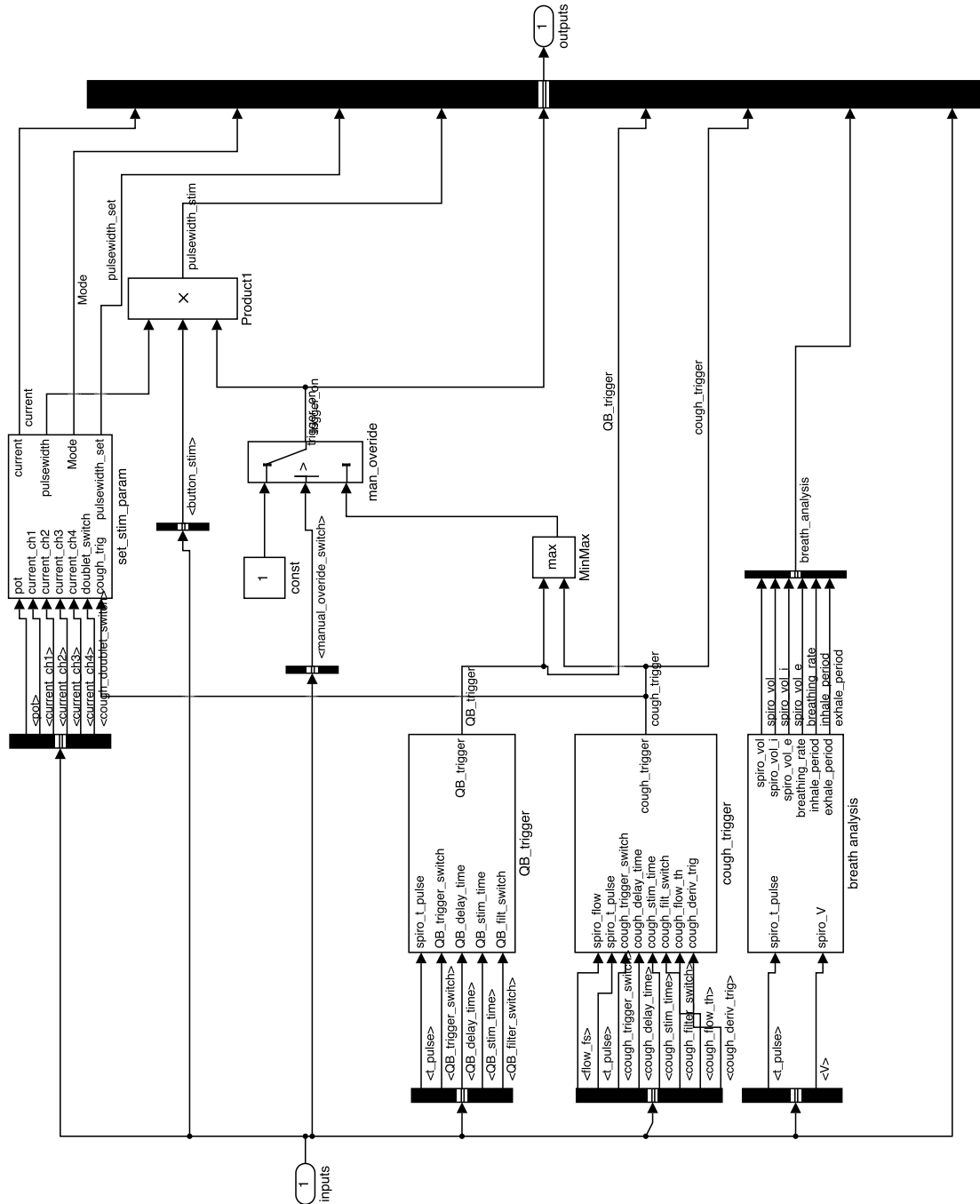
Figure A.9: Assessment/Process.mdl
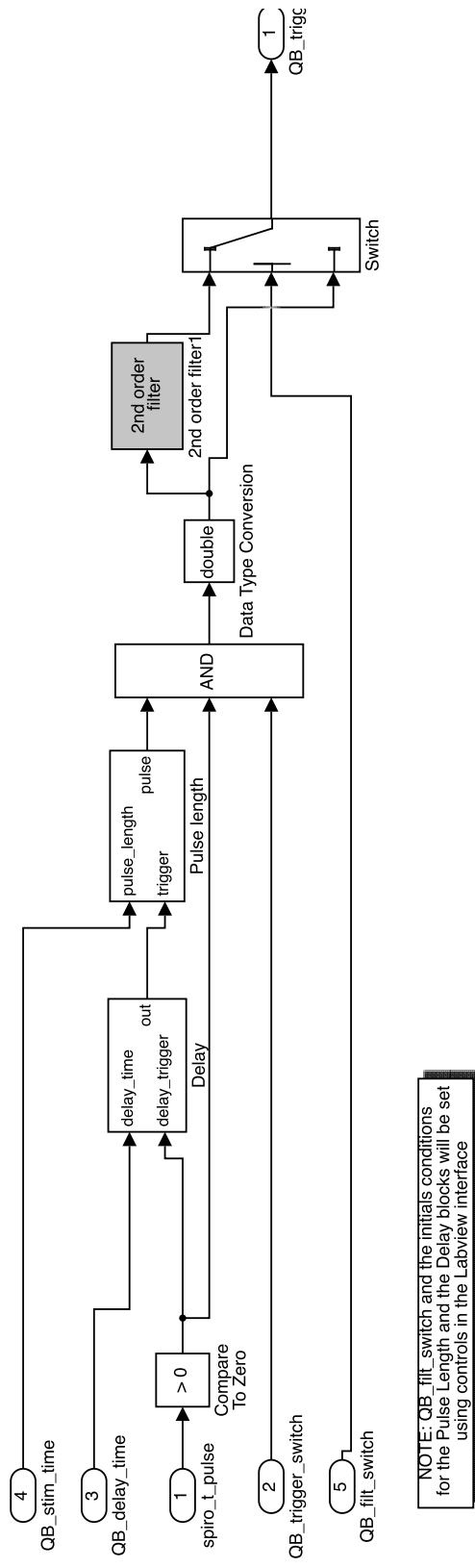
Figure A.10: Assessment/Process/QB_trigger.mdl

Table A.10: Block parameters for Assessment/Process/QB_trigger.mdl shown in Figure A.10

Name	Type	Parameter	Value	Note
Compare To Zero	Compare To Zero	Operator	>	-
Delay	Sub-function	-	-	Figure A.11
Pulse length	Sub-function	-	-	Figure A.12
AND	Logical Operator	Operator	AND	
Data Type Conversion	Data Type Conversion	Output data type	Double	
2nd Order Filter	Sub-function	-	-	Figure A.13
Switch	Switch	Criteria	u2 $\geq$ Threshold	
		Threshold	0.5	

Figure A.11: Assessment/Process/QB_trigger/Delay.mdl

Table A.11: Block parameters for Assessment/Process/QB_trigger/Delay.mdl shown in Figure A.11

Name	Type	Parameter	Value	Note
-1	Constant	Value	-1	
pulse length	DiscreteIntegrator	Gain	1	
		External reset	rising	
		Initial condition source	external	
0	Constant	Value	0	
≤	Relational Operator	Relational operator	≤	
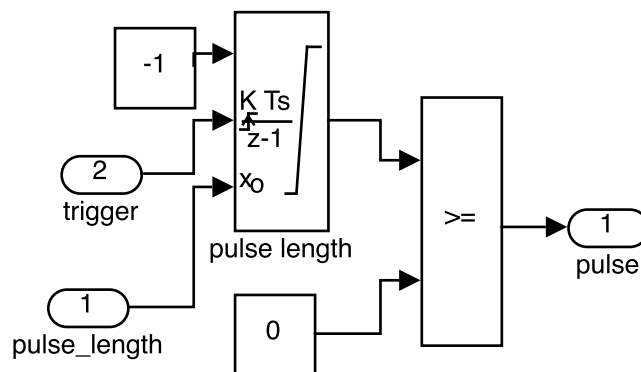
Figure A.12: Assessment/Process/QB_trigger/Pulse Length.mdl

Table A.12: Block parameters for Assessment/Process/QB_trigger/Pulse length.mdl shown in Figure A.12

Name	Type	Parameter	Value	Note
-1	Constant	Value	-1	
pulse length	DiscreteIntegrator	Gain	1	
		External reset	rising	
		Initial condition source	external	
0	Constant	Value	0	
$\leq$	Relational Operator	Relational operator	$\leq$	
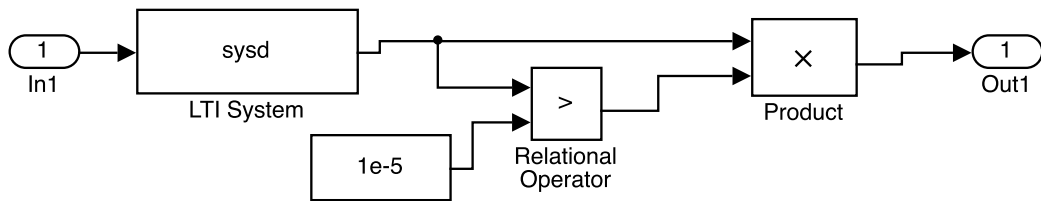
Figure A.13: Assessment/Process/QB_trigger/Pulse Length/2nd order filter.mdl

Table A.13: Block parameters for Assessment/Process/QB_trigger/2nd order filter.mdl shown in Figure A.13. This block was masked with the following initialisation commands: wn=1.8/tr; xi=0.99; sys=tf(wn^2,[1 2*xi*wn wn^2]); sysd = c2d(sys,Ts); The mask had two dialog variables: tr was set to 0.1 for all subjects; Ts was the model sample time (0.02)

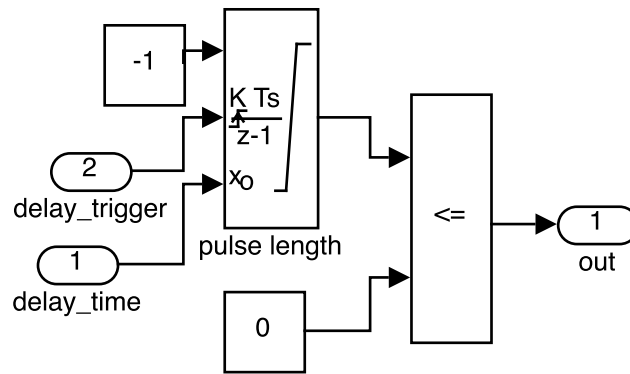| Name	Type	Parameter	Value	Note
LTI System	LTI Block	system variable	sysd	
1e-5	Constant	Value	1e-5	
Relational Operator	Relational Operator	>		
Product	Product	-	-	Defaults used

Figure A.14: Assessment/Process/cough_trigger.mdl

Table A.14: Block parameters for Assessment/Process/cough_trigger.mdl shown in Figure A.14.

Name	Type	Parameter	Value	Note
Insp Flow	Sub-function	-	-	Figure A.15
derivative threshold	Sub-function	-	-	Figure A.16
trigger if...	Logical Operator	Operator	AND	
Delay	Sub-function	-	-	Figure A.17
Pulse length	Sub-function	-	-	Figure A.18
AND	Logical Operator	Operator	AND	
Data Type Conversion	Data Type Conversion	Output data type	double	
Gain	Gain	Gain	1.2	
2nd order filter	Sub-function	-	-	Figure A.13
Switch	Switch	Criteria	u2 $\geq$ Threshold	
		Threshold	0.5	
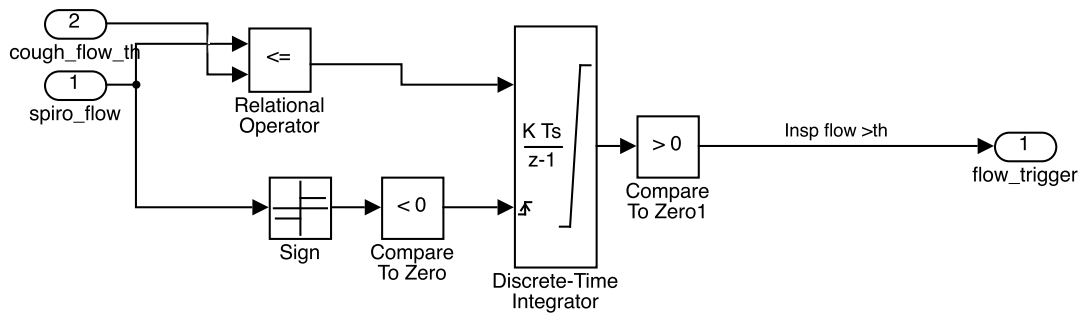
Figure A.15: Assessment/Process/cough_trigger/Insp Flow.mdl
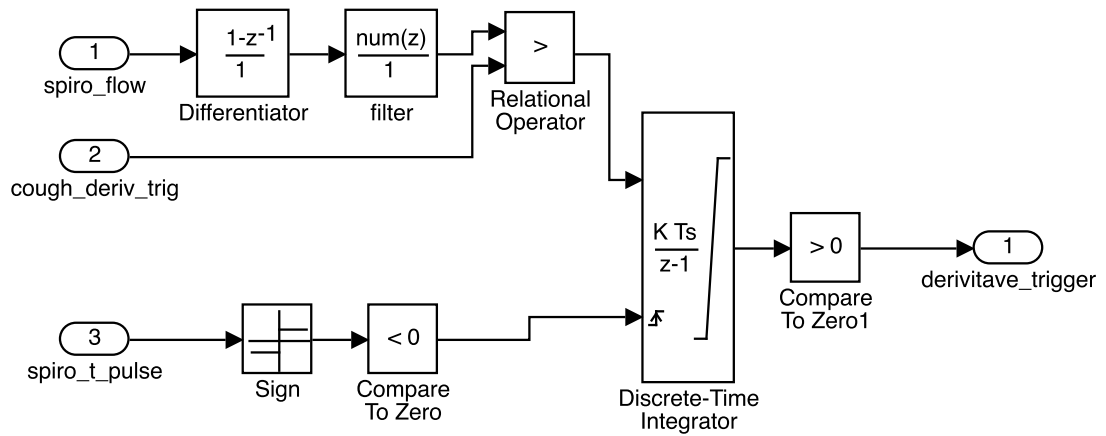
Figure A.16: Assessment/Process/cough_trigger/derivative threshold.mdl

Table A.15: Block parameters for Assessment/Process/cough_trigger/Insp Flow.mdl shown in Figure A.15

Name	Type	Parameter	Value	Note
≤	Relational Operator	Relational operator	≤	
Sign	Signum	-	-	Defaults used
Compare To Zero	Compare To Zero	Operator	<	
-1	Constant	Value	-1	
Discrete–Time Integrator	DiscreteIntegrator	Gain	1	
		External reset	rising	
		Initial condition source	internal	
		Initial condition	0	
Compare To Zero	Compare To Zero	Operator	>	

Table A.16: Block parameters for Assessment/Process/cough_trigger/derivative threshold.mdl shown in Figure A.16

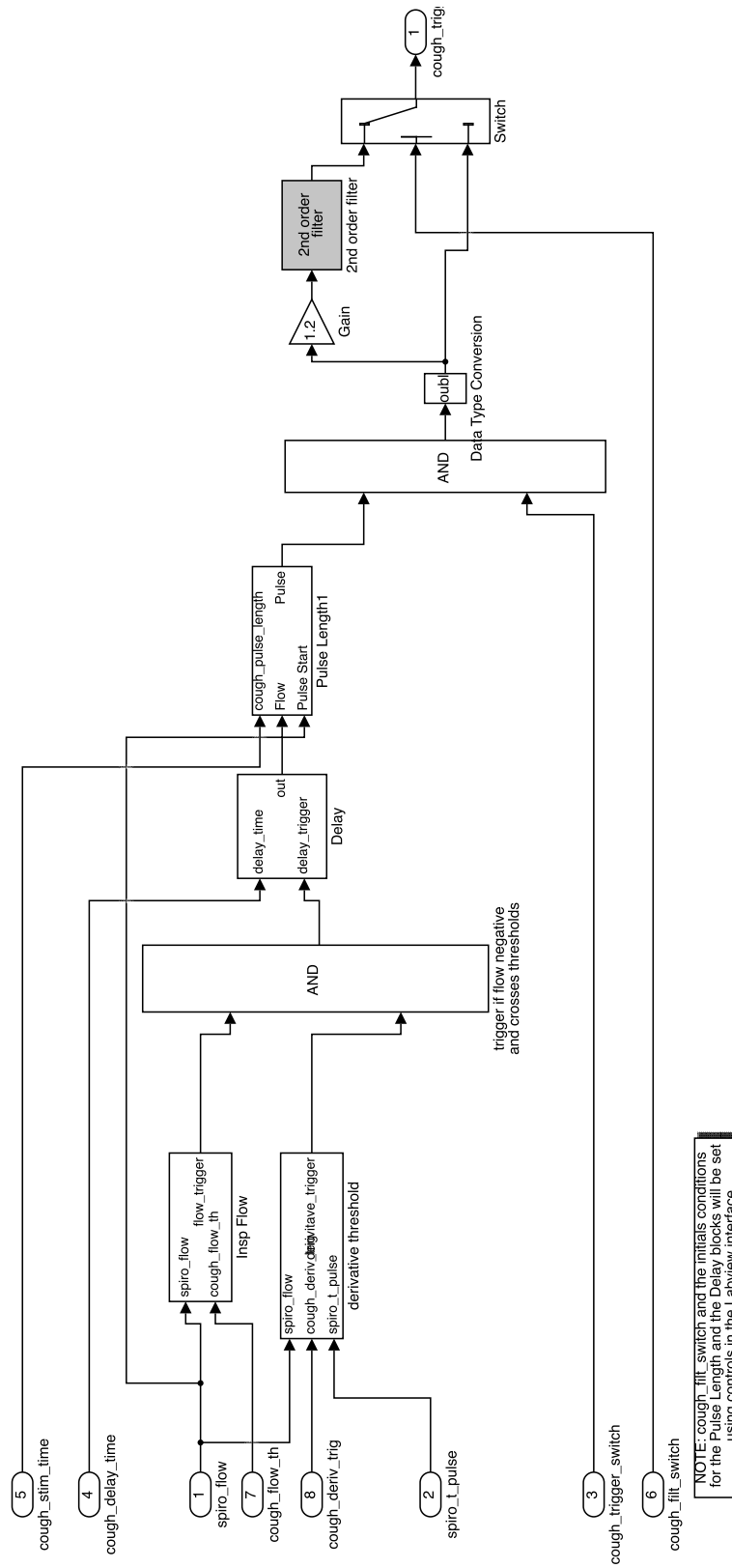| Name	Type	Parameter	Value	Note
Differentiator	Discrete Filter	Numerator	[1 -1]	
		Denominator	[1]	
filter	Discrete Filter	Numerator	1/5*[1 1 1 1 1]	
		Denominator	[1]	
Relational Operator	Relational Operator	operator	>	
Sign	Signum	-	-	Defaults used
Compare To Zero	Compare To Zero	Operator	<	
Discrete-Time Integrator	DiscreteIntegrator	Gain	1	
		External reset	rising	
		Initial condition source	internal	
		Initial condition	0	
Compare To Zero1	Compare To Zero	Operator	>	
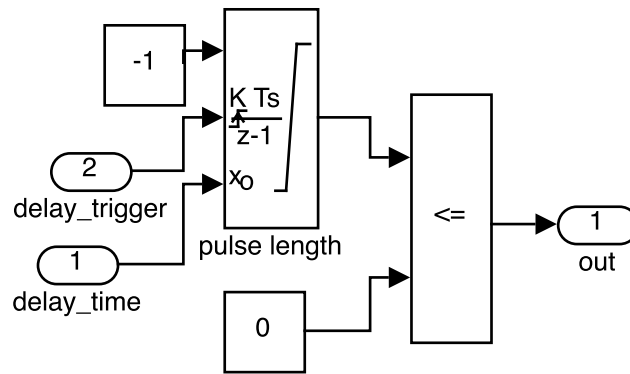
Figure A.17: Assessment/Process/cough_trigger/Delay.mdl

Table A.17: Block parameters for Assessment/Process/cough_trigger/Delay.mdl shown in Figure A.17

Name	Type	Parameter	Value	Note
-1	Constant	Value	-1	
pulse length	DiscreteIntegrator	Gain	1	
		External reset	rising	
		Initial condition source	external	
0	Constant	Value	0	
≤	Relational Operator	Relational operator	≤	
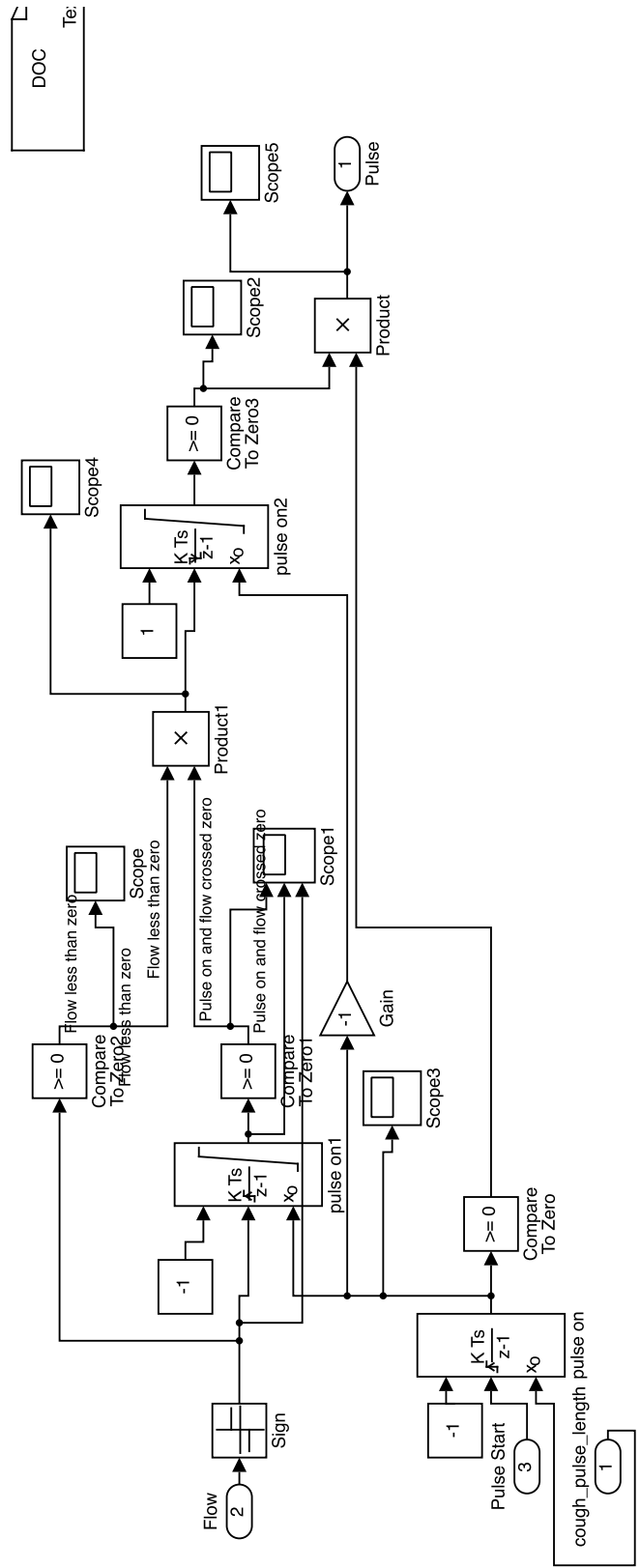
Figure A.18: Assessment/Process/cough_trigger/Pulse Length.mdl

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Table A.18: Block parameters for Assessment/Process/cough.trigger/Pulse Length1.mdl shown in Figure A.18

Name	Type	Parameter	Value	Note
-1	Constant	Value	-1	
pulse on	DiscreteIntegrator	Gain	1	
		External reset	rising	
		Initial condition source	external	
Compare to Zero	Compare To Zero	operator	$\geq$	
Sign	signum	-	-	Defaults used
-1	Constant	Value	-1	
pulse on1	DiscreteIntegrator	Gain	1	
		External reset	rising	
		Initial condition source	external	
Compare to Zero1	Compare To Zero	operator	$\geq$	
Compare to Zero2	Compare To Zero	operator	$\geq$	
Gain	Gain	Gain	-1	
Product1	Product	-	-	Defaults used
1	Constant	Value	1	
pulse on2	DiscreteIntegrator	Gain	1	
		External reset	falling	
		Initial condition source	external	
Compare to Zero3	Compare To Zero	operator	$\geq$	
Product	Product	-	-	Defaults used

Figure A.19: Assessment/Process/breath analysis.mdl

Table A.19: Block parameters for Assessment/Process/breath_analysis shown in Figure A.19

Name	Type	Parameter	Value	Note
exhalation_start	Compare To Zero	operator	$\geq$	
inhalation_start	Compare To Zero	operator	$<$	
volume_inhale_reset	Sample and Hold	Trigger type	Rising edge	
volume_exhale_reset	Sample and Hold	Trigger type	Rising edge	
Add	Sum	List of signs	-+	
Add1	Sum	List of signs	-+	
Gain	Gain	Gain	2	
Product	Product	-	-	Defaults used
Product1	Product	-	-	Defaults used
Product2	Product	-	-	Defaults used
Add2	Sum	List of signs	+1	
calculate_breathing_rate	Sub-function	-	-	Figure A.20
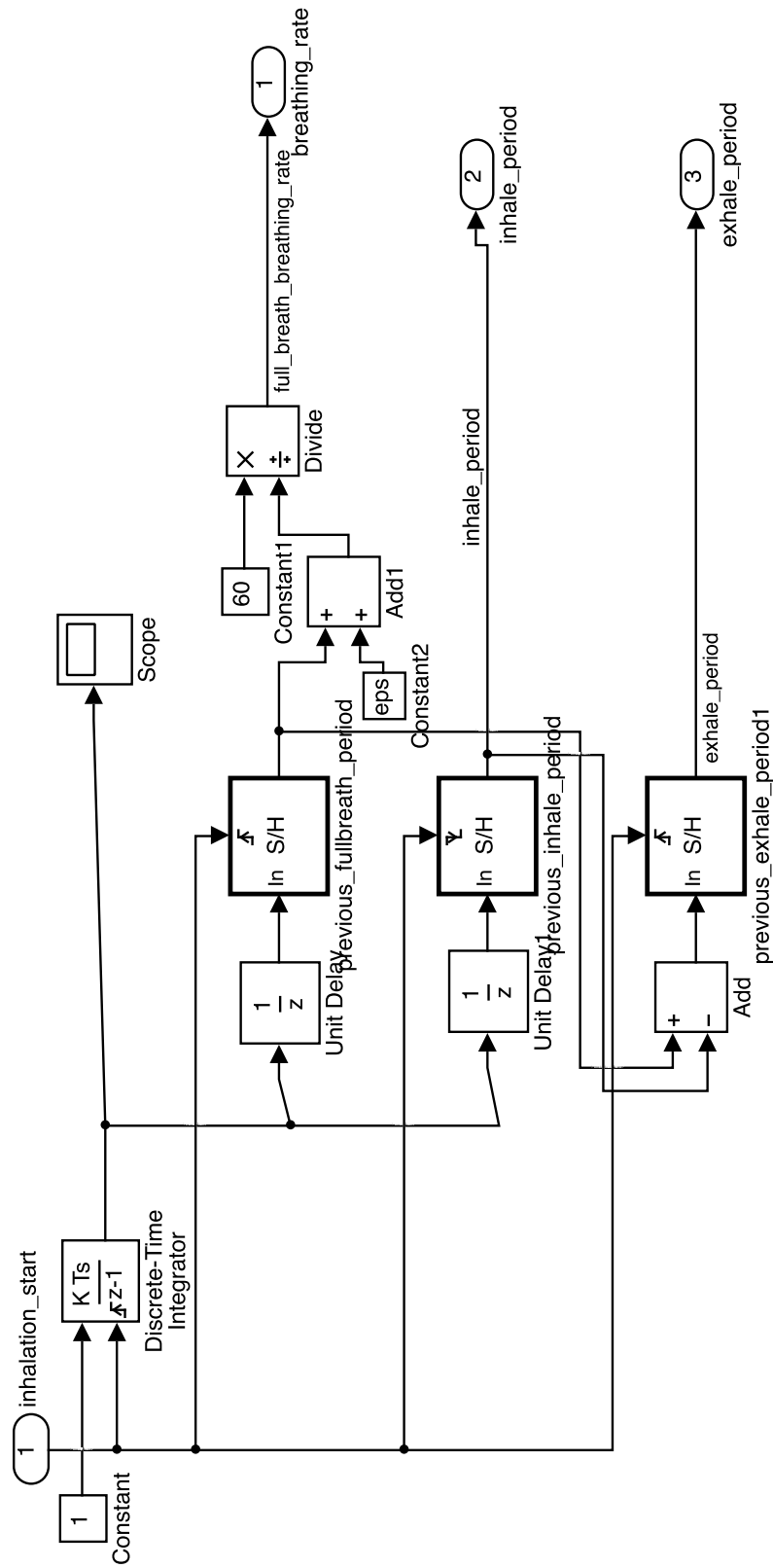
Figure A.20: Assessment/Process/breath analysis/calculate_breathing_rate.mdl

Table A.20: Block parameters for Assessment/Process/calculate_breathing_rate shown in Figure A.19

Name	Type	Parameter	Value	Note
Constant	Constant	Value	1	
Discrete–Time Integer	DiscreteIntegrator	Gain	1	
		External reset	rising	
		Internal condition source	internal	
		Initial condition	0	
Unit Delay	Unit Delay	Initial Condition	0	
previous_fullbreath_period	Sample and Hold	Trigger type	Rising edge	
Unit Delay1	Unit Delay	Initial Condition	0	
previous_inhale_period	Sample and Hold	Trigger type	Falling edge	
Add	Sum	List of signs	+-	
previous_exhale_period1	Sample and Hold	Trigger type	Rising edge	
Constant2	Constant	Value	eps	
Add1	Sum	List of signs	++	
Constant1	Constant	Value	60	
Divide	Product	Number of Inputs	*/	
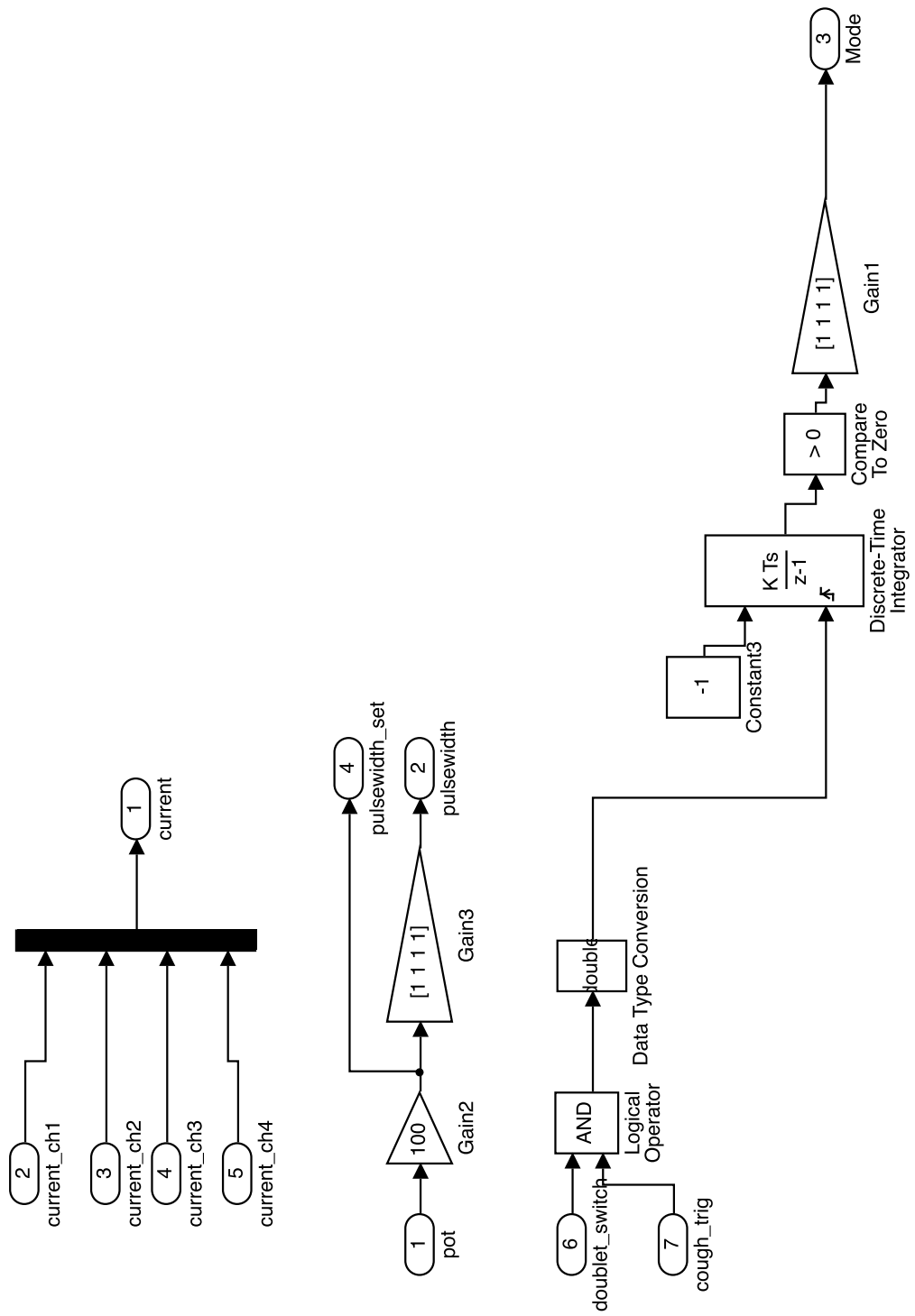
Figure A.21: Assessment/Process/set_stim_param.mdl

Table A.21: Block parameters for Assessment/Process/set_stim_param shown in Figure A.21

Name	Type	Parameter	Value	Note
Gain2	Gain	Gain	100	
Gain3	Gain	Gain	[1 1 1 1]	
Logical Operator	Logical Operator	Operator	AND	
Data type Conversion	Data Type Conversion	Output data type	double	
Constant3	Constant	Value	-1	
Discrete-Time Integrator	DiscreteIntegrator	Gain	1	
		External reset	rising	
		Initial condition source	internal	
		Initial condition	0.02	
Compare To Zero	Compare To Zero	Operator	>	
Gain1	Gain	Gain	[1 1 1 1]	
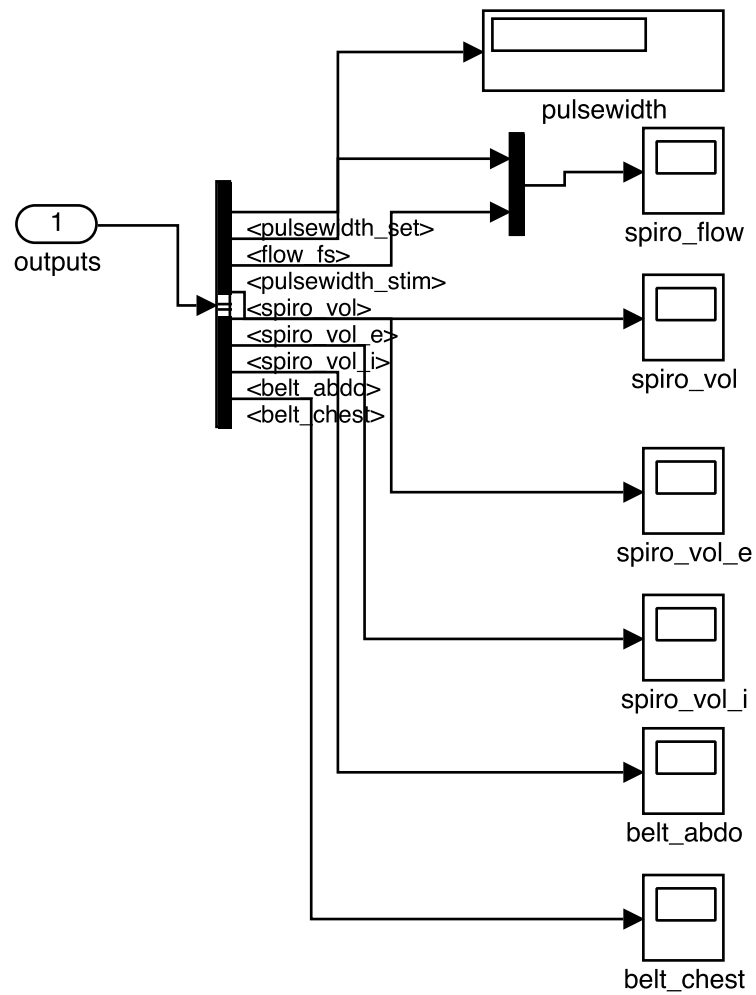
Figure A.22: Assessment/Process/debug.mdl
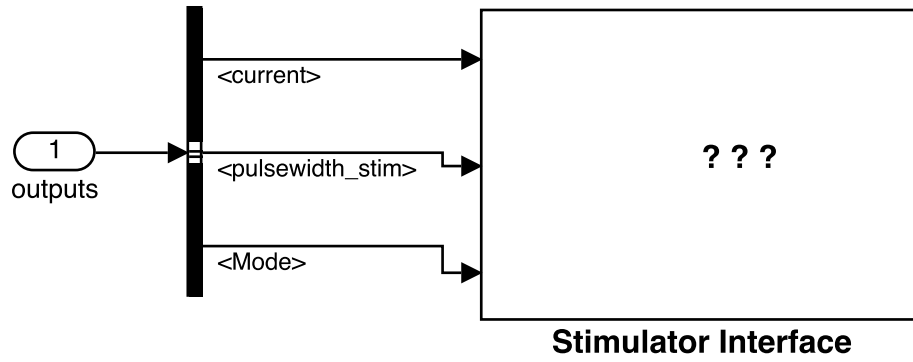
Figure A.23: Assessment/Process/to_hardware.mdl

Table A.22: Block parameters for Assessment/to_hardware shown in Figure A.23

Name	Type	Parameter	Value	Note
Stimulator Interface	S-function	Channels to be Stimulated	[1 2 5 6]	S-function written by H. Gollee
		Main Time	33	
		Group Time	6	
		Enable doublets	True	
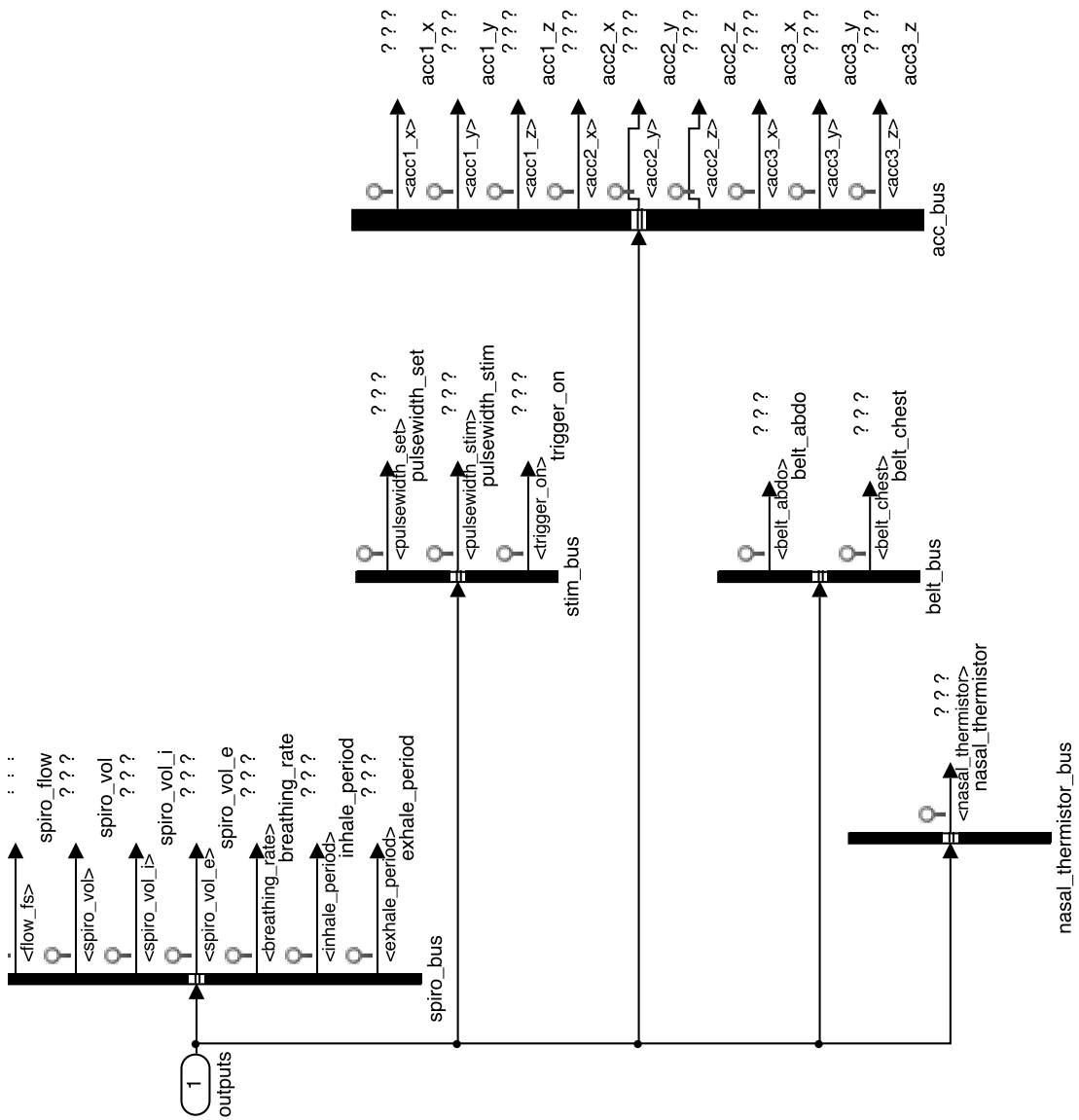
Figure A.24: Assessment/Process/to_labview.mdl
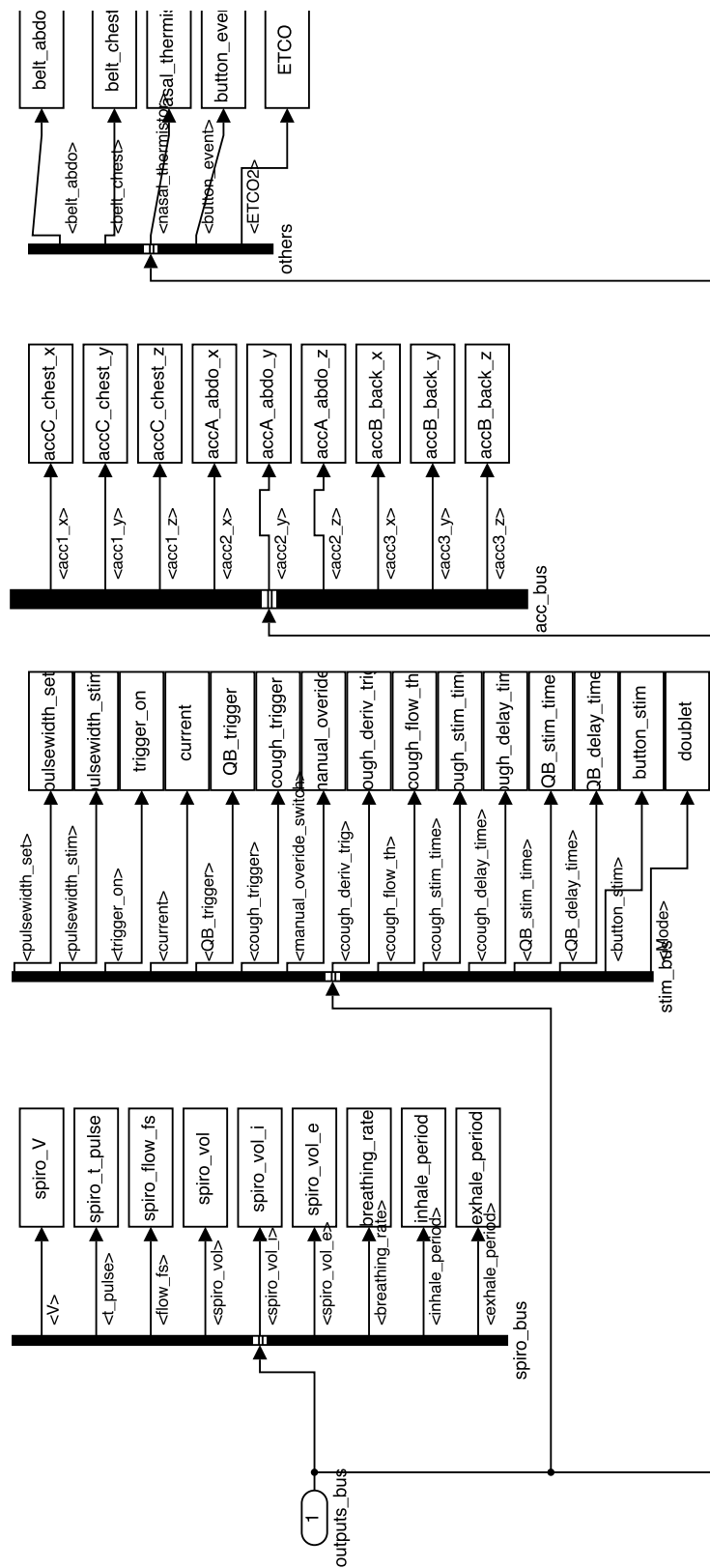
Figure A.25: Assessment/Process/save_data.mdl. Each of the blocks in this diagram were To Workspace blocks with the Variable name as shown in the Figure and the save format set to Array.

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[1] Empi Continuum Product Webpage.

[2] Odstock Product Page.

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