Work of Breathing in Exercise and Disease
By Tom Powell

“A submission presented in partial fulfilment of the requirements of the University of Glamorgan/Prifysgol Morgannwg for the degree of Doctor of Philosophy.”

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Abstract

This thesis is focussed on developing new methods and outcomes to assess respiratory function that require little or no volitional effort on behalf of the participants being tested. Specifically to attempt to detach the behaviour of the patient from the accuracy of the test of respiratory function, resulting in techniques that are simpler and easier to administer and undertake for both assessor and participant. It aims to develop methods that reduce the involvement of the participant during assessment of respiratory function. The human body’s way of controlling respiration has evolved into a sophisticated system that optimises breathing pattern to maintain the most efficient homeostatic action of the respiratory system. Eliciting and assessing this automatic response is the key to removing the action of participation from respiratory function testing. The focus must therefore be on developing non-invasive, sub-maximal techniques that allow participants to enter into a steady state of respiration and how this can be assessed.

Two techniques were investigated; Respiratory Endurance (as the inspiratory work of breathing) and Tidal Breathing Flow Profile, and these were successfully applied in 99 adult participants (68 healthy controls and 31 COPD patients) and 75 children (48 clinical group and 27 healthy controls) who completed 467 respiratory endurance trials whilst seated and exercising, and 249 relaxed tidal breathing trials.

The difficulties with lung function assessment are well established and have been described in this thesis. Much recent emphasis has been put on developing existing devices and protocols rather than developing new techniques and approaching these difficulties from alternative viewpoints. This thesis has described the development of innovative techniques to assess the function of the respiratory systems that aim to overcome the issues associated with maximal testing. It was shown that these techniques are easy to undertake for a range of participants, simple to analyse and are able to reliably differentiate between health and disease, suggesting that they could become a useful adjunct to existing methods of respiratory assessment.
Acknowledgments

This thesis would not have been possible without the help and support I received from many people over the past 3 years. In particular I would like to thank:

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The participants who gave up their time and effort to involve themselves in the studies that form my thesis.

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My family and friends, for their love and support, in particular my partner Zoe and son Joshua.

Finally, I would like to express my thanks and appreciation to Dr Mark Williams, my director of studies, advisor and mentor, without whose help, input and faith in me, I would not have completed this thesis.
Authors Declaration

I declare the work in this thesis was carried out in accordance with the regulations of the University of Glamorgan/Prifysgol Morgannwg. The work is original except where acknowledged or indicated by special reference in the text. No part of this thesis has been submitted for any other degree.

Any views expressed in the thesis are those of the author and in no way represent those of the University of Glamorgan/Prifysgol Morgannwg.

The dissertation has not been presented to any other University for examination in the United Kingdom or overseas.

Signed

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<td>6MWD</td>
<td>Six minute Walk Distance</td>
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<tr>
<td>6MWT</td>
<td>Six minute Walk Test</td>
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<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
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<td>ARTP</td>
<td>Association of Respiratory Technology and Physiology</td>
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<td>ATS</td>
<td>American Thoracic Society</td>
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<tr>
<td>BE</td>
<td>Breathing Endurance</td>
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<td>British Thoracic Society</td>
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<tr>
<td>CF</td>
<td>Cystic Fibrosis</td>
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<tr>
<td>CLD</td>
<td>Chronic Lung Disease (of Prematurity)</td>
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<tr>
<td>cmH$_2$O</td>
<td>Centimetre of Water</td>
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<tr>
<td>CO$_2$</td>
<td>Carbon Dioxide</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<tr>
<td>CROP</td>
<td>Chronic Respiratory disease Of Prematurity study (CROP)</td>
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<td>ECSC</td>
<td>European Community for Steel and Coal</td>
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<td>ERS</td>
<td>European Respiratory Society</td>
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<tr>
<td>FEV$_1$(L)</td>
<td>Forced Expiratory Volume in 1 Second</td>
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<tr>
<td>FEV$_1$TAP(L)</td>
<td>Forced Expiratory Volume in 1 Second Predicted by Tidal Airway Profile</td>
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<td>f$_H$(bpm$^{-1}$)</td>
<td>Heart Rate</td>
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<td>f$_R$(min$^{-1}$)</td>
<td>Respiratory Rate</td>
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<tr>
<td>FRC (L)</td>
<td>Functional Residual Capacity</td>
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<td>FVC (L)</td>
<td>Forced Vital Capacity</td>
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<td>GOLD</td>
<td>Global Initiative for Chronic Lung Disease</td>
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<tr>
<td>IME</td>
<td>Inspiratory Muscle Endurance</td>
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<tr>
<td>InWrs$^{mouth}$(J.L)</td>
<td>Inspiratory Work of Breathing Measured at the Mouth</td>
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<tr>
<td>kPa</td>
<td>Kilopascal</td>
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<tr>
<td>mmHg</td>
<td>Millimetre of Mercury</td>
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<tr>
<td>MSVC</td>
<td>Maximal Sustainable Ventilatory Capacity</td>
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<td>MVV</td>
<td>Maximal Voluntary Ventilation</td>
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<td>O$_2$</td>
<td>Oxygen</td>
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<td>PaCO$_2$</td>
<td>Partial Pressures of CO$_2$</td>
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<td>PaO$_2$</td>
<td>Partial Pressures of O$_2$</td>
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<td>PTEF</td>
<td>Peak Tidal Expiratory Flow</td>
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<td>R$_{AW}$</td>
<td>Intrinsic Airway Resistance</td>
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<td>RIP</td>
<td>Respiratory Inductance Plethysmography</td>
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<td>R$_K$(kPa.L.sec$^{-1}$)</td>
<td>Constant Applied Resistive Load</td>
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<td>Respiratory Muscle Analyser</td>
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<td>RV (L)</td>
<td>Residual Volume</td>
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<td>Sustainable Inspiratory Pressure</td>
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<td>TBFV</td>
<td>Tidal Breathing Flow Volume</td>
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<td>TBPA</td>
<td>Tidal Breathing Profile Analysis</td>
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<tr>
<td>tE</td>
<td>Time of Expiration</td>
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<tr>
<td>tEND</td>
<td>Time to Trial End</td>
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<tr>
<td>tI</td>
<td>Time of Inspiration</td>
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<tr>
<td>tI/tTot</td>
<td>Time of Inspiration Over Total Breath Time</td>
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<tr>
<td>TLC (L)</td>
<td>Total Lung Capacity</td>
</tr>
<tr>
<td>tPFTEF</td>
<td>Time to Peak Tidal Expiratory Flow</td>
</tr>
<tr>
<td>tTot</td>
<td>Total Breath Time</td>
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<td>UHW</td>
<td>University Hospital of Wales</td>
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<td>( \dot{V}_E )</td>
<td>Minute Ventilation</td>
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<td>VME</td>
<td>Ventilatory Muscle Endurance</td>
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<tr>
<td>( \dot{V}CO_2 )</td>
<td>Carbon Dioxide Production</td>
</tr>
<tr>
<td>( \dot{VO}_2 )</td>
<td>Oxygen Uptake</td>
</tr>
<tr>
<td>( \dot{VO}_2 \text{ max (ml.kg.min}^{-1} )</td>
<td>Maximal Volume of Oxygen Uptake During Maximal Aerobic Exercise</td>
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<td>VT (L)</td>
<td>Tidal Volume</td>
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<td>VTi (L)</td>
<td>Tidal Volume on Inspiration</td>
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<td>VTi/tI(L.sec(^{-1}))</td>
<td>Tidal Volume on Inspiration Over Time of Inspiration</td>
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<td>WE</td>
<td>Energy on Expiration</td>
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<tr>
<td>WI</td>
<td>Energy on Inspiration</td>
</tr>
<tr>
<td>WI/tI(J.sec(^{-1}))</td>
<td>Energy on Inspiration Over Time of Inspiration</td>
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<td>WOB</td>
<td>Work of Breathing</td>
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Chapter 1 - Introduction

1.0 Study Aims and Overview
Breathing is truly a strange phenomenon of life, caught midway between the conscious and unconscious (Richards 1957) and is reactive to voluntary and involuntary control, making assessment of the respiratory system a complex task. The function of the respiratory system can be assessed using a variety of methods that represent the functional capability as part of the overall physiological status of an individual. Nowhere else in medicine does the patient need to be considered, whole and entire, as in the field of respiration (Richards 1957). The ability to measure respiratory function parameters has been available for clinical use for approximately the last 40 years (ARTP 2006), yet the respiratory muscles and the mechanics of breathing have engaged the interest of the great anatomists and physicians (Rankin & Dempsey 1967) from the time of Galen, da Vinci and beyond (Fig 1.1).
The incidence of respiratory disorders due to degenerative muscle conditions, obesity and lung diseases such as Chronic Obstructive Pulmonary Disease (COPD), asthma and chronic bronchitis is gradually increasing in the modern world (Ratnovsky et al 2008). The use of suitable measures of respiratory function is therefore important not only for the clinical treatment of patients, but to also accurately assess disease prevalence which in turn informs healthcare policy. Existing methods such as spirometry have been the focus of much attention and research, and are now established as ‘gold standard’ measurements and rightly so. This thesis does not contend that this should not be the case, or that other more suitable techniques exist. However, it is proposed that in certain circumstances and situations, principally when these existing methods cannot be correctly employed, that there exists a potential for new techniques to be developed to overcome such situations so that respiratory function can be adequately assessed.

Unlike other techniques which measure other physiological functions such as blood pressure or ECG, the majority of respiratory measurements rely on substantial levels of volitional cooperation from a participant to attain acceptable results. Even with a highly experienced respiratory physiologist with correctly functioning and calibrated equipment, without the cooperation of the participant to follow instruction, a correct result will not be achieved. It may be argued that it is the skill of the respiratory physiologist to overcome any reluctance to participate by a patient and that therefore
Correct technique can always be achieved. Calverley (2009) describes spirometry as ‘in many senses effort independent, providing the subject makes a reasonable attempt’. In essence Calverley is suggesting that spirometry is effort independent as long as a participant tries hard enough, which is a misnomer. This encapsulates the major issue with respiratory measurement in that many who practice it expect everyone participating to 1) want to undertake it and 2) try to complete it as well as possible. While they may agree to the former they may not, or cannot, do the latter.

While most children above the age of 7–8 yrs can successfully complete the respiratory function tests available for adults, assessing younger children is more involved, due to the lack of suitable equipment and the complexity of undertaking such measurements (Merkus et al 2005), although it has been shown that even pre-school children are able to successfully complete spirometry (Eigen et al 2001). Techniques to improve the feasibility of respiratory function testing in children include creating a playful environment, adaptation to a shorter attention span and ‘considerable patience’ (Gappa et al 2006). Again, while it can be argued that with sufficient training, practice and time, accurate and reliable results can be performed, this is so that full cooperation can be obtained, not that accurate results can be achieved without it. The natural extension to this argument is to the example of infants, where many standard respiratory function tests cannot be undertaken as they cannot follow instruction. This indicates that above all, full cooperation is vital for correct and accurate completion of standard respiratory function tests.

It is not just children where there may be issues with successfully completing respiratory tests. Groups such as the elderly, individuals with learning disabilities or chest disease patients experiencing acute exacerbations of their symptoms, may struggle to follow instruction and may also not be able to always complete specific respiratory tests. Indeed patients may be less coordinated and motivated than healthy subjects (Romer & McConnell 2004).

Furthermore respiratory measurement also involves considerable effort, Enright & Lehman (2009) describe how most ‘diagnostic tests require little or no maximal activity by a patient in order to obtain good quality results, conversely spirometry requires a rapid sequence of three unusually athletic-type breathing manoeuvres’.
Accurate assessment of maximal inspiratory pressure (MIP) can require up to 20 repeated maximal tests (Wen et al 1997). What other forms of human diagnostic testing require such repetition and maximal effort on behalf of the participant as that associated with respiratory testing?

This thesis is focussed on developing new methods and outcomes to assess respiratory function that require little or no volitional effort on behalf of the participants being tested. Specifically to attempt to detach the behaviour of the patient from the accuracy of the test of respiratory function, resulting in techniques that are simpler and easier to administer and undertake for both tester and participant.

Chapter 1 reviews how breathing is regulated, describes the respiratory muscles and outlines approaches to measuring respiratory function.

Chapter 2 synthesises the existing literature in relation to Respiratory Endurance and Tidal Breathing Profile Analysis (TBPA)

Chapter 3 describes the methodology used in subsequent chapters

Chapter 4 outlines the development of a 6-minute protocol to assess Respiratory Endurance

Chapter 5 tests the repeatability and reliability of these measures of Respiratory Endurance and TBPA

Chapter 6 assesses how measures of Respiratory Endurance react during exercise

Chapter 7 measures Respiratory Endurance and TBPA in COPD

Chapter 8 measures Respiratory Endurance and TBPA in Children

Chapter 9 outlines a new method of resistive load detection in health and disease

Chapter 10 summarises the work in this thesis

Chapter 11 provides a conclusion to the work in this thesis and future directions of research.
1.1 Structure and Function of the Respiratory System

The principal function of the human respiratory system is the exchange of the respiratory gases O\textsubscript{2} and CO\textsubscript{2}, which maintains adequate levels of O\textsubscript{2} in the arterial blood so that the metabolic demands of the body can be met (Braman 1995). This process can be described as ventilation. The respiratory system (Fig 1.2) consists of the lungs, airways, chest wall, respiratory muscles and rib cage, and the parts of the central nervous system that regulate breathing (Cloutier 2007).

The lungs, located within the thoracic cage, are the organs of ventilation where the exchange of gas takes place. Ventilation consists of rhythmic changes in lung volume and during spontaneous breathing the lungs passively follow the changes in the contours of the thorax produced by the contraction of the respiratory muscles (Nunn 1993). Breathing, like cardiac activity must be sustained at an adequate level to meet the demands placed upon it throughout life (Celli 1989).

Figure 1.2: Structure of the lungs (downloaded www.northhertsradiologygroup.co.uk)

The movement of gas in and out of the lungs, or ventilation, is performed by the respiratory muscles (Ratnovsky et al 2008) which generate a pressure gradient so that on contraction of the inspiratory muscles, a negative pressure is generated and gas
flows into the lungs. During exhalation the inspiratory muscles relax, the pressure inside the chest and airways increases and gas flows passively out of the lungs (Fig 1.3). To promote the flow of gas the architecture of the respiratory tree is such that air flows with very little resistance, although this can be increased in many disease states (Zechman et al 1957). The respiratory muscles therefore perform the crucial function of sustaining ventilation (Moxham 2000) by generating the pressure gradient necessary for the movement of gas.

![Respiration diagram](image)

**Fig 1.3: Respiration (Copyright Encyclopaedia Britannica 2006)**

As ventilation of the lungs eliminates CO₂ from the body and promotes the addition of O₂ to the blood it thereby controls the partial pressures of O₂ (PaO₂) and CO₂ (PaCO₂) as well as the pH of arterial blood. When the respiratory system is disrupted by a change in PaO₂ or PaCO₂ the change is sensed by receptors resulting in a change in the breathing pattern to maintain homeostasis (Braman 1995). The control of breathing, while able to be temporarily overcome by conscious control for example breath holding or when talking or singing, is a powerful automatic mechanism that will take ultimately involuntary control to preserve homeostasis (Section 1.5).
1.2 Control and Regulation of Ventilation

Although breathing is a rhythmic process with no intrinsic driving system, respiration requires external neural drive to maintain adequate ventilation. Ventilation is regulated by the levels of CO\(_2\) and O\(_2\) and the pH of the blood and has been reviewed fully elsewhere (Braman 1995), and can be summarised as comprising of three components: the control centre; the sensors; and the effectors organs (Fig 1.4). Like every control system it needs various components for it to function control, these include a control variable, a desired value for that variable, a measured value for that variable, sensors to detect the measured variable, effectors to change the system to maintain the desired variable and a control system. Both the rate and depth of breathing are controlled to maintain PaCO\(_2\) close to 40mmHg, even during periods of activity, rest or sleep, arterial PaCO\(_2\) is held at 40 ±2-3mmHg (Cloutier 2007).

**Figure 1.4: The Control of Respiration**

The respiratory control centres are located in several areas of the brainstem, the most important being the medulla oblongata where respiratory rhythm originates (Nunn 1993). The rhythmicity is generated within specific areas of the medulla oblongata, the dorsal respiratory group (DRG), ventral respiratory group (VRG) and Botzinger complex. Neurons in the cerebral cortex also contribute and can override the automatic control system for voluntary respiratory efforts such as breath holding (Braman 1995) although these can only be sustained for short periods of time.

The sensors that control breathing consist of chemoreceptor’s (central and peripheral) and the mechanoreceptors which all function to maintain homeostatic levels of arterial PaO\(_2\) and PaCO\(_2\). Central chemoreceptor’s in the medulla oblongata react to changes in CO\(_2\) and pH in the cerebrospinal fluid (CSF), whereas peripheral chemoreceptor’s
in the aortic arch respond to changes in O$_2$, CO$_2$ and pH (Richardson 2003). The mechanoreceptors are located within the airways and chest wall such as within the intercostal muscles and diaphragm and give protective reflexes affecting bronchomotor tone. Of these sensors it is the central chemoreceptors that are the most important stimulus of breathing, detecting change in the CSF by way of hydrogen ion concentration due to increases in PaCO$_2$. Ventilation increases almost linearly with changes in hydrogen ion concentration thus CO$_2$ in the blood regulates breathing by way of its effect on the pH of the CSF fluid (Cloutier 2007). Changes in arterial pH take longer to influence the CSF as the hydrogen ions cross the blood brain barrier too slowly to affect the central chemoreceptors.

1.3 Muscles of Respiration

Ventilation requires a coordination of the respiratory muscles which create change in the shape of the thoracic cage creating the necessary pressure gradient so that gas moves in and out of the lungs. While the complexity of some of the movements and muscle insertions is such that the mechanical action of individual muscles can hardly be determined with precision (Rankin & Dempsey 1967), the respiratory muscles can be divided into two groups. Those that are active on inspiration, performing most of the work of breathing at rest, and the expiratory muscles which are largely inactive only being used when exhalation becomes active such as during exercise or other situations when the ventilatory system is stressed (Celli 1989). Many of the respiratory muscles are involved in other motor functions, including coughing, sneezing, retching swallowing and postural adjustments of the trunk and chest wall (Rowley et al 2005).

The respiratory muscles can be broadly categorised as a ventilatory pump and are centred around the diaphragm (Celli 1989), the dome shaped skeletal muscle that contracts downwards and outwards like a piston increasing the size of the thoracic cavity (ARTP 2006) creating the negative pressure gradient required for inspiration. The respiratory muscles are skeletal muscles and ability of the force of contraction increases on being stretched and decreases on being shortened, thus the force of contraction increases with increasing lung volume (Cloutier 2007). As diaphragmatic function becomes compromised, such as when ventilation or resistance to breathing is increased, additional inspiratory muscles and eventually expiratory muscles are recruited to provide the work of breathing (Nunn 1993).
The diaphragm is the most important inspiratory muscle, with motor innervations solely from Phrenic nerves (C3, 4, 5) (Nunn 1993). Like other skeletal muscle it is composed of three fibre types and corresponding motor types which vary in their physiological and histochemical properties, slow twitch, fast twitch oxidative and fast twitch glycolytic, with an obvious trade off with sustained increased ventilatory effort and fatigue susceptibility of fast twitch motor units. Therefore it is not only important to determine maximal strength of respiratory muscle but also the endurance capabilities (Belman & Sieck 1982). It has been shown that the diaphragm is able to remodel in response to chronic overload, consisting of fibre type transfer and increased oxidative capacity (Dempsey 2006). The accessory muscles of respiration include the Intercostals, abdominal muscles, Scalenes and Sternocleidomastoids (Rankin et al 1967; Ratnovsky et al 2008).

1.4 Respiratory Homeostasis

Homeostasis is the physiological process by which the human body maintains the internal systems of the body in equilibrium despite variations in external conditions (Martin 2004). As discussed previously (Section 1.3) the control of breathing has evolved into a highly sophisticated, negative feedback system which is able to accurately match the level of ventilation with the requirements of the body. Individuals appear to select one particular breathing pattern among the infinite number of possible combinations of ventilatory variables and airflow profiles (Benchetrit 2000) that enables the work of breathing to be minimised (Cloutier 2007). This process is an automatic unconscious one, in that when left alone individuals will find the most efficient breathing pattern for the ventilation level required. Even with additional stress or loads if these are not immediately fatiguing and remain constant the respiratory control system will adopt the most efficient pattern of breathing to accommodate. Although in healthy subjects the pattern of breathing can vary they can be approximately described as normal values (Fig 1.5).
Table 1.1: Normal Breathing Patterns - Values of Healthy Individuals (adapted from Cloutier 2007)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>Respiratory Rate - $f_R$</td>
<td>12 (bpm$^{-1}$)</td>
</tr>
<tr>
<td>Tidal Volume – $V_T$</td>
<td>0.5 (L$^1$)</td>
</tr>
<tr>
<td>Minute Ventilation - $\dot{V}_e = f_R \times V_T$</td>
<td>$0.5 \times 12 = 6$ (L.min$^{-1}$)</td>
</tr>
<tr>
<td>Total Lung Capacity – TLC</td>
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1.5 Existing Techniques to Assess Respiratory Function

Respiratory function measurements are made to obtain objective information about the health and structure of the airways and/or lungs. Many standard techniques exist that assess respiratory function and are used to quantify the health and ability of the lungs (BTS 1994). The assessment of respiratory function is now a routine part of clinical practice with many specialised laboratories in the UK with international guidelines being established for the standardisation of spirometry (Miller et al 2005). Clinically, forced expiratory volumes measured with spirometry (Section 3.4) is the key tool in lung function testing (Miller 2009) and can be used to differentiate between health and disease, and to assess disease severity (Section 7.1).

Methods of testing the respiratory system are invaluable as screening tests of general respiratory health in the same way that blood pressure provides important information about general cardiovascular health (Miller et al 2005) and for the use in clinical management of respiratory disease. For example spirometry is used within international guidelines to assess disease severity such as those for COPD (Gomez 2002) and subsequent onset of medical treatment.

1.5.1 Spirometry

Spirometry is the most commonly performed respiratory function test, although alone it cannot define the full extent of respiratory disease (ARTP 2006). Originally assessed using water sealed spirometers that can be precisely calibrated by the displacement of water (Nunn 1993) modern versions of the device use sophisticated electronics to integrate air flow with time to give lung volumes. Spirometry involves making a series of maximal manoeuvres (normally 3) that reflect a complex, dynamic relationship between patient effort, muscle strength, compliance and elastic recoil of...
the lungs as well as airway resistance. Standard pulmonary function tests such as spirometry and static lung volumes require a certain level of respiratory muscle strength (Rochester 1988) and coordination to be completed successfully.

1.5.2 Maximal Static Pressures

The assessment of maximal pressures has been reviewed elsewhere (Black & Hyatt 1969), and are used to represent the strength of the respiratory muscles. In clinical practice respiratory muscle force is indirectly measured through the pressure generated at the mouth during inspiration (MIP or $P_{I,max}$) or expiration (MEP or $P_{E,max}$) and is expressed as kilopascal (kPa) or cm water (cmH$_2$O) (1 kPa=10.2cm H$_2$O) and represent pressure changes generated against atmospheric pressure (Troosters et al 2005). Up to twenty attempts may be needed to obtain an acceptable result although a respiratory warm up may reduce MIP variability (Volianitis et al 2001), reducing the need for so many attempts. Furthermore because maximum respiratory pressures are indices of maximal strength they are highly effort independent and require well-motivated participants (McConnell 2007). MIP tests are tiring and subjects should be allowed several minutes rest between maximal efforts, despite careful coaching some subjects simply are unable to coordinate adequately to perform MIP and MEP manoeuvres (Rochester 1988).

1.6 Issues Affecting Respiratory Function Testing

When completed correctly spirometry is the gold standard method for assessing respiratory function. The main issue when assessing respiratory function is that of error in the result. This is important as results obtained are used to inform clinical decisions or act as key outcomes in research studies. Reducing or removal of the error is the key aim in maintaining the accuracy of respiratory measurement. Sources of error can include:

1.6.1 Equipment

Accurate measurement and assessment of respiratory function can require expensive, highly technical equipment that does not react well to being moved. More portable devices have been developed but there can be a decrease in accuracy. Respiratory devices like all diagnostic equipment require frequent calibration to maintain accuracy.

1.6.2 Staff

Fully trained and experienced clinical respiratory physiologists are required to conduct testing to gain accurate results. Individuals that only occasionally conduct
respiratory assessments will not have the same level of expertise or experience as those working in specialist centres performing testing on a regular basis.

1.6.3 Environment
The need for highly specialised centres means that most respiratory function testing is centred on units based in large hospitals. Testing away from these sites with equipment and staff, can mean accuracy falls. Wensley & Silverman (2001) report a steady decrease in spirometric values made at home in asthmatic children even over a relatively short 4 week period. Other studies of peak expiratory flow again in asthmatic children have found that many of the home recordings were in fact ‘self-invented’ i.e. not blown but a value recorded anyway in a diary (Kamps et al 2001).

1.6.4 Participant
As has already been argued (Section 1.1) it is the participant that has the biggest effect on sources of error, principally because the individual conducting the test has no direct control over the actions of the participant. There is also a learning effect that accompanies all volitional tests of respiratory function (Eastwood et al 1998).

1.7 Initial Research Focus
The focus of this thesis is to develop new methods of assessing respiratory function that can reduce the influence of patient behaviour that can affect test outcome. While this cannot totally be removed; participants must still consent to take part/breathe through a device for example, it is the removal of active participation which is the goal, much like other diagnostic tests such as blood pressure or an ECG for example.

This thesis aims to find a new way of assessing respiratory function based around existing work on expiratory flow profiles (Colsanti et al 2004) as a review of the literature (Section 2.3) suggests that this may be a way of assessing respiratory function without the need for full participation in respiratory manoeuvres.

Additionally this thesis will focus on testing of the endurance of the respiratory system. As breathing is a continuous process, measures of respiratory strength (MIP) appear inappropriate for assessing endurance, provoking the question what is respiratory endurance and can techniques be developed that accurately measure it?

These aims can be addressed as part of two themes:

1) The Participant: How well do participants complete any new methods?
2) The Test: How well do these new methods represent respiratory function?
1.8 Respiratory Muscle Testing

Over the last twenty years efforts have been made to develop techniques to assess respiratory muscle function (ATS 2002) however the ability to evaluate the respiratory muscles is limited because of their inaccessibility (Clanton & Diaz 1995) making them difficult to assess, and the techniques employed are still relatively primitive (Nava 1998). All-inclusive functions of the respiratory muscles is an important index in diagnosis and follow up treatment of breathing problems, due to respiratory weakness (Ratnovsky et al 2008).

Previously, measures of respiratory function have been indirectly used to assess the respiratory muscles on the basis that some indices are affected in part by the respiratory muscles (Romer & McConnell 2004). However unlike lung function which can be predicted with reasonable accuracy on the basis of stature, gender and age, (Coates 1993) respiratory muscle function shows much less predictability, making one-off measurements largely meaningless unless there is underlying gross weakness (McConnell 2007).

With few exceptions respiratory muscle function testing involves the whole respiratory pump system (Celli 1989). At advanced stages of obstructive airway disease, thoracic resistive diseases or neuromuscular disorders, respiratory failure may occur due to either, increasing the work of breathing beyond the muscle endurance capacity or a weakening of the muscle that cannot sustain the work of normal, quiet breathing (Ratnovsky et al 2008). Failure of the lung parenchyma leads to hypoxaemia, although acute hypercapnia may ensue if there insufficient functioning gas exchange tissue to eliminate CO₂. Failure of the ventilatory pump and in particular a dysfunction of the respiratory muscles leads to hypercapnic respiratory failure (Nava 1998). Failure of the respiratory muscles can also lead to dyspnoea¹.

1.8.1 Respiratory Muscle Strength

Not only is there a wide natural variation in muscle strength between individuals (Moxham 2000), there is also a much greater degree of intra subject variability in maximal respiratory pressures than in other pulmonary function tests (Rochester

¹ As the spelling of dyspnea/dyspnoea varies due to the American/British origin of an author I will use irrespective of the original spelling the British version ‘Dyspnoea’ as given in the Oxford Concise Medical Dictionary (Martin 2004)
Respiratory muscle strength can be assessed using pressure measurement at the mouth although this only estimates global performance of respiratory muscles (Ratnovsky et al 2008). However these maximal respiratory muscle pressures can also be recorded within the pleural and abdominal cavities with balloon catheters inserted via the nose and the pharynx into the oesophagus for pleural pressure and into the stomach for abdominal pressure (Rochester 1988) although invasive testing has inherent risks (Section 1.12). Strength is determined by muscle fibre density, the pattern of innervation, the pre contraction length and the velocity of muscle fibre shortening. Endurance depends on all these properties but also upon other properties such as mitochondrial mass, myoglobin content, capillary density, arterial oxygenation and the level of cardiovascular fitness (Aldrich 1985).

1.8.2 Respiratory Muscle Endurance

Though in normal humans there are only a few occasions when the reserve of respiratory muscle function is utilised sufficiently to cause fatigue, there are certain groups of patients where the endurance properties of the respiratory muscles may be critical to survival or necessary for adequate exercise tolerance (Clanton 1995). With the increased use of pulmonary rehabilitation programmes it is necessary to monitor endurance performance rather than strength and valid measures of endurance are needed to assess the outcomes of such interventions (Powell & Williams 2009).

Despite intense investigation the importance of respiratory muscle endurance in the failing patient or the obstructed patient during exercise is still relatively inadequate, just as important are the development of better techniques for evaluating respiratory muscle endurance and work capacity in chest disease patients (Clanton 1995).

1.9 Fatigue Versus Endurance

Endurance is a term that when applied to skeletal muscle is synonymous with resistance to fatigue (Clanton 1995). To be explicit, endurance and fatigue do not represent the same concept and to use the terms in this way is incorrect.

Failure or fatigue is a definite point that can be easily identified and measured. Respiratory muscle fatigue can be described as occurring when respiratory endurance is exceeded (Nava 1998). The inability to sustain adequate ventilation at rest is an extreme example of respiratory muscle fatigue (Belman & Sieck 1982).
Muscle endurance is the ability to sustain a specific muscular task over time (ATS 2002A). The undefined time component is the most important aspect as, unlike exercise endurance which when exceeded merely results in the cessation of the exercise, exceeding respiratory endurance resulting in fatigue can result in the cessation of breathing.

Therefore in the context of respiration, respiratory endurance refers to the ability of the respiratory muscles to sustain respiration indefinitely. The use of ambiguous terms such as fatigability (Belman & Sieck 1982B) can been seen in the wider literature and makes the differential between endurance and fatigue difficult. In those articles identified in the literature synthesis (Section 2.2.5) that attempt to make a definition, endurance is often framed as a property that affords resistance to fatigue.

Although they appear related, endurance cannot be accurately predicted from estimates of maximal ventilatory pressures, capacity or strength (ATS 2002A). Endurance should be viewed as a continuous ongoing process, whereas fatigue is the definite point when the ability to endure has failed. Endurance (from the Latin duro or durare - to make hard, last out, to survive) is best defined as the ability to resist fatigue or exhaustion (from fatigo or fatigaio – to weary, tire or to be overcome) (Morwood 1994). The two terms are not interchangeable.

1.10 Maximal Versus Sub-Maximal / Incremental Versus Constant
While a measure of fatigue provides valuable information about an individual’s maximum capacity, it does not measure the clinically important ability of the respiratory system to endure sub-maximal loads such as those experienced during the physical activities of daily life. In terms of physical exercise testing, within the latest ATS/ACCP statement on cardio respiratory testing it states ‘while incremental protocols are widely used in clinical practice, constant work rate protocols are gaining popularity because of their clinical ability, particularly for assessing response to therapy and other interventions’ (ATS/ACCP 2003).

To assess the endurance of the respiratory system, constant loading of the respiratory muscles may be more appropriate since pathologies such as airway narrowing or obstruction, chest wall restriction, or muscle weakness are constant rather than progressing ‘loads’ (Rohrbach et al. 2003). While breathing against a resistance,
mechanisms of load compensation induce adaptations in the pattern of breathing proportional to the applied load (Calabrese et al. 1998) and these changes act to maintain ventilation at the most optimum or efficient level (Zechman et al. 1957).

Incremental tasks reflect the strength rather than the endurance of the respiratory muscles (Eastwood et al. 1994). Completing a test to fatigue/exhaustion will result in a participant being unable to achieve a level of optimum efficiency as they will have to continually adapt to the increased load being placed upon them. They will feel a significant level of distress and discomfort and it requires a high degree of cooperation to reach such a maximal point.

Such maximal tests are volitional in nature, requiring participant motivation, which make it difficult to establish whether it is a respiratory impairment or inadequate effort that is responsible for poor test performance (Moxham 2000). Sustained and incremental load protocols define the point of respiratory fatigue/exhaustion when a participant can no longer continue. This is not a measure of respiratory endurance. Endurance assessment protocols that allow participants to adapt to the most efficient homeostatic breathing response would represent the best measure of endurance.

1.11 Invasive Versus Non-Invasive Testing

Any form of invasive testing involves some form of inherent risk to the patient. It requires a ‘step-up’ in terms of clinical environment, equipment and personnel required to safely undertake procedures. In addition invasive techniques require a fully cooperative and willing subject. Measurement of oesophageal and gastric pressures aid the study of diaphragm, although these remain a research tool (Celli 1989) perhaps due to their unsuitability for widespread use in clinical practice. Direct measurements of respiratory muscle activity are still considered basic physiology and are not utilised in clinical settings (Ratnovsky et al 2008).

As a key aim of this thesis is on developing new methods of assessing respiratory function that require little or no volitional effort on behalf of the participants, invasive testing methods would be contrary to this. Furthermore if any new methods are to be developed an additional aim would be to use them in the sub-clinical and home environment where it would be inappropriate to undertake protocols that incorporate some form of invasive procedure.
1.12 Work\(^2\) of Breathing

During inspiration the muscles of breathing work against three main types of forces; 1) the elastic forces developed in the tissues of the lung and thorax when volume change occurs; 2) flow resistive forces that depend on frictional resistance to airflow; and 3) inertial forces which depend on the mass and acceleration of tissues and gases (Rankin & Dempsey 1967). Work of breathing is the change in volume times the pressure exerted across the respiratory system and is composed of elastic and non elastic components, and is elevated in individuals with chronic pulmonary disease (Cloutier 2007).

When expiration is passive during quiet breathing, the work of breathing is performed entirely by the inspiratory muscles. Approximately half of this work is dissipated during inspiration as heat in overcoming frictional forces opposing inspiration, the other half stored as potential energy in the deformed elastic tissues of lung and chest wall (Nunn 1993). Inspiratory work is consistently larger than expiratory work; with the inspiratory muscles developing a higher rate of flow and therefore a higher pressure that accounts for the additional work during inspiration (Cain & Otis 1949). Patients with severe COPD must expend many times more energy to breathe than normal subjects, even at rest their respiratory muscles must work harder than normal in order to compensate for airway obstruction present (Aldrich 1985).

Work of breathing may be studied by measuring either the total energy required by the respiratory muscles or the mechanical work done by them (Rankin & Dempsey 1967). The complete assessment of the work of breathing is complex as quantifying movement and distortions of the chest wall are difficult to quantify and as such work of breathing measured at the mouth is not a direct measure of the work of breathing. However ‘measuring the work performed against an external load can provide sufficient information for purposes of respiratory endurance testing’ (ATS 2002\(^A\)).

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\(^2\) Work of breathing is equal to the product of the mean volume and the mean change in pressure whereas power is a measure of the rate at which work is being performed. The term work of breathing is widely used but power is the correct term (Nunn 1993 Pp124)
1.13 Summary & Development of Research question(s)

In Summary……..

In this chapter I described and summarised the respiratory system and the concepts of respiratory endurance and fatigue.

The Participant

- The human respiratory system will always if allowed, adopt the most efficient breathing pattern for the work imposed upon it.
- Full cooperation from a motivated participant is required to successfully complete most respiratory tests.
- Not all participants can successfully complete all standard lung function tests.

The Test

- Endurance and fatigue are individual concepts that cannot be used interchangeably.
- Fatiguing test protocols cannot measure respiratory endurance.
- Using the homeostatic response of the breathing control system can allow resting breathing patterns to be achieved.

This thesis aims to develop methods that reduce the involvement of the participant during assessment of respiratory function. While using invasive techniques may be able to accomplish this, by their very nature they do not lend themselves to widespread use, with the inherent problems of invasive procedures and do not match with the simple approach to respiratory measurement set out at the start of this thesis (Section 1.1). The human body’s way of controlling respiration has evolved into a sophisticated system that optimises breathing pattern to maintain the most efficient homeostatic action of the respiratory system. Eliciting and assessing this automatic response is the key to removing the action of participation from respiratory function testing. The focus must therefore be on developing non-invasive, sub-maximal techniques that allow participants to enter into a steady state of respiration and how this can be assessed.

Therefore the initial research questions are:

1. Using the concept of endurance as being a constant function, can respiratory endurance be accurately measured? Specifically what other techniques have been
described to assess respiratory muscle endurance and do they follow the concept of endurance as a constant sub-maximal state?

2. Can the work of Colsanti et al (2004) be used as a sub-maximal technique to accurately predict lung volumes, specifically FEV₁?
Chapter 2 - Review of the Literature

2.0 Introduction and Overview


2.2 Review of Respiratory Muscle Endurance (RME)

2.3 Review of Peak Tidal Expiratory Flow (PTEF) Measurement

2.4 Summary & Conclusions

2.0 Introduction and Overview

This chapter reviews the literature in relation to respiratory endurance assessment and tidal breathing profile analysis that form the general focus of the thesis, the sub-maximal, non-invasive assessment of respiratory function. It begins with an overview of the syntheses of the literature and the conceptual framework behind it. The first section (2.2) details a review of non-invasive techniques available for measuring Respiratory Muscle Endurance (RME). The second section (2.3) reviews the technique of using tidal breathing airflow profile to predict FEV₁ called Tidal Breathing Profile Analysis – TBPA (described later in section 3.2). TBPA has been developed by only one group (Colsanti et al 2004), the review of the literature for this topic therefore looks at the basis of generating the airflow data and the main parameter calculated, Peak Tidal Expiratory Flow (PTEF). These results are then summarised and used to inform the future work of the thesis.


Research is rarely conducted in an intellectual vacuum and it therefore needs to be securely grounded and explored within the context of the existing base of knowledge. This results from the previous work of other research studies within the same or similar field(s). It is not always clear what a review of the literature implies, most frequently it relates to the gathering of existing work, whereas a synthesis of the literature or research explicitly implies some form of critical appraisal and evaluation that denote an active process rather than a collation of information. Davies (2004) and Depoy & Gitlin (1994) both list the major reasons why a critical synthesis of the literature is important that can be summarised as; identifying the context in which the topic is being explored, outlining what is known about the topic, reviewing the level and relevance of relevant theory and knowledge development, and formulating the rationale for the selection of research strategy.
Cooper (1998) gives a framework for the process of synthesis namely, problem formulation stage, data collection/literature review, data evaluation, analysis and interpretations, and public presentation. However, Polit & Beck (2008) illustrate a more in-depth example of this process, this conceptualisation provides a more detailed approach that actively encourages feedback mechanisms into the overall strategy and more importantly, active reflection on the part of the reviewer or synthesiser. This synthesis of current research will apply this model emphasising the use of feedback mechanisms, for example cross referencing publication lists in ‘new’ articles with those currently held to ensure all relevant articles are located – and developing new search strategies such as related search terms and locations for possible articles.

2.2 RME: Original Research Question

Using the concept of endurance being a constant function, can respiratory endurance be accurately measured? Specifically what other techniques have been described to assess respiratory muscle endurance and do they follow the concept of endurance as a constant sub-maximal state?

2.2.1 Redefinition of the Research Question.

To facilitate the synthesis of the existing literature in the context of developing a synthesis rather than a simple review of the literature it was necessary to adapt the original research question to meet the needs outlined in section 2.1. The original question needed to be adapted to become more specific and to identify its key components and definable ways of answering these;

1. What is RME?
   - What does it represent? Practically and physiologically

2. How has RME been defined?
   - What issues or difficulties can be identified?

3. How has RME been measured?
   - In what groups of individuals?
   - In what environments?
   - With what devices and protocols?
2.2.2 Formulation of Search Strategy

The search strategy was as follows:

1. Search term Respiratory Muscle Endurance
2. Format of literature Original research studies published in peer reviewed academic journals and books (symposiums)
   Relevant academic journals (see Section 2.2.3)
4. Selection criteria Articles were identified by the appearance of the search term in either the article title or the body of any abstract
5. Inclusion/Exclusion criteria Described a non-invasive method of assessing RME Related to human physiology In English
   Full Article, not personal communication or conference abstract
   Available to reviewer as either paper or electronic copy
6. Other Sources Relevant Academic Journals

Figure 2.1: RME search strategy

Key respiratory journals and other scientific journals that had published papers identified in this review and that were available to the reviewer (Table 2.1) were regularly checked for relevant recent articles using selection criteria listed above (Appendix 2.1).

2.2.3 Results of Article Search

Initial searching with the ‘Respiratory Muscle Endurance’ search term yielded sixty-two articles that fulfilled the inclusion/exclusion criteria. However on initial appraisal of these articles it became apparent that alternate terms were being used to describe or represent RME, in many circumstances interchangeably. The most common alternative term that was used was Inspiratory Muscle Endurance (Scherer et al 2000; Koppers et al 2006A 2000B; Chang et al 2005; Morrison et al 1989A; Weiner et al 1998A 1998B; Tobin et al 2002; van der Esch et al 2004; and Walsh et al 1996). However Ventilatory Muscle Endurance (Eastwood et al 2001; Morgan et al 1987)
The initial search was therefore repeated using the following key terms 1) Inspiratory Muscle Endurance 2) Ventilatory Muscle Endurance and 3) Breathing Endurance. In total 110 journal articles were identified (Table 2.2). Each article was critically appraised for; terms and definitions used; study design; sample size; subject group; assessment method; and assessment results. The results were then tabulated (Appendix 2.2).

2.2.4 Range of Academic Journal Sources and Year of Publication

Articles appeared in a range of journals across a variety of academic disciplines including respiratory medicine, applied physiology, sports medicine, cardio-vascular disease, and paediatric sciences, indicating the wide interest in respiratory endurance within the scientific community. Chest, the journal of the American College of Chest Physicians was responsible for publishing the largest number of journals that fulfilled the synthesis inclusion criteria (Fig 2.2).

Search databases used for this review varied in the chronological length of their search, ZETOC (from 1993), EMBASE (from 1974) and MEDLINE (from 1949), PubMed indexes MEDLINE so shares a similar earliest available record. The earliest article that fulfilled study criteria was published in 1976. In the past 20 years there has been a regular publication of relevant papers at 4.5 per year (Fig 2.3).

2.2.5 A Clear Description of Respiratory Endurance

The variation in the terms applied to non-invasive respiratory endurance measurement has been highlighted (Section 2.2.3). Not only do studies refer to RME, Inspiratory Muscle Endurance (IME), Ventilatory Muscle Endurance (VME) and Breathing Endurance (BE), it is not unusual for these terms to be used interchangeably; RME & IME (Chang et al 2005; Inzelberg et al 2005; Morrison et al 1989; Sette et al 1997; Tobin et al 2002; Walsh et al 1996; and Weiner et al 1998), RME & VME (Martin et al 1986; and Eastwood et al 2001) and RME & BE (Williams et al 2002).
### Table 2.1: Relevant Academic Journals Reviewed

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Applied Physiology</th>
<th>Sport &amp; Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorax</td>
<td>Journal Applied Physiology</td>
<td>Medicine Science in Sport Exercise</td>
</tr>
<tr>
<td>Chest</td>
<td>European Journal Applied Physiology</td>
<td>British Journal Sport Medicine</td>
</tr>
<tr>
<td>Chronic Respiratory Disease</td>
<td></td>
<td>International Journal Sport Medicine</td>
</tr>
<tr>
<td>Respiratory Medicine</td>
<td></td>
<td>Journal Science Medicine Sport</td>
</tr>
<tr>
<td>European Respiratory Journal</td>
<td></td>
<td>Journal Sport Science</td>
</tr>
<tr>
<td>Respiration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Physiology &amp; Neurobiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Journal Respiratory Critical Care Medicine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2.2: Search Terms and Number of Articles Located

<table>
<thead>
<tr>
<th></th>
<th>Respiratory Muscle Endurance</th>
<th>Inspiratory Muscle Endurance</th>
<th>Ventilatory Muscle Endurance</th>
<th>Breathing Endurance</th>
<th>Journal search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total articles</td>
<td>62</td>
<td>44</td>
<td>20</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Invasive method</td>
<td>3</td>
<td>8</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Commentary</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Review</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>33</td>
<td>18</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Grand Total</td>
<td>110</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 2.2: Scientific Journals Publishing Papers in this Review

Figure 2.3: Chronological Output of Papers
This variation is most probably due to the complexity of ‘endurance’ and what it involves (see Section 1.9). The common use of the term IME could be due to the fact that at rest expiration is a passive process and the work of breathing is performed by the inspiratory muscles (Nunn 1993). Whereas VME relates to the methods that utilise increased levels of ventilation as their indices of endurance. Despite these factors the range of terms and their interchangeable use as it appears in the scientific literature represents poor scientific practice and such variation and disparities should be a focus particularly on behalf of journal publishers and reviewers when assessing future work.

This poor use of terminology is further compounded by the infrequent use of clearly stated definitions. Of the 110 articles identified only 15 explicitly defined a measure of endurance (Table 2.3). These definitions were either; loose or simplistic descriptions of endurance; standard physiological measures that were used as indices; or were based on the modality of the test employed. None attempted to explicitly define endurance in biological or physiological terms.

In addition the majority of articles that relate to non-invasive methods of assessing respiratory endurance include the term ‘muscle’ i.e. respiratory muscle endurance, inspiratory muscle endurance etc. Therefore these articles suggest or imply that the technique or method they employ is capable of measuring the capabilities of the respiratory muscles. However when measurements are made at the mouth as non-invasive tests must do by definition, it is difficult to directly assess the respiratory muscles per se, or to isolate their action from that of other respiratory system components. More accurately it is the function of the entire respiratory system that is being assessed, including elastic recoil of the lungs and the chest wall structure, in combination with the respiratory muscles.

Therefore when measuring endurance non-invasively at the mouth it is inaccurate to refer to the respiratory muscles with respect to any definition. A term that regards the respiratory system as a whole would be more accurate and therefore more preferable. It could be suggested ‘Respiratory System Endurance’ or ‘Respiratory Endurance’ as a preferable term. In the rest of this synthesis however, when assessing individual articles the term that the article authors use will be used accordingly.
<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Term used</th>
<th>Stated Definition (descriptive)</th>
<th>Author &amp; Year</th>
<th>Term used</th>
<th>Stated Definition (relating to test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scherer et al. 2000</td>
<td>Respiratory muscle endurance (RET)</td>
<td>RET = sustained ventilation RMT</td>
<td>Fiz et al. 1998</td>
<td>Respiratory Muscle Endurance</td>
<td>1. IME = maximum tolerated load for a 2min incremental Martyn test (C&lt;sub&gt;max&lt;/sub&gt;)</td>
</tr>
<tr>
<td>Mueller et al. 2006</td>
<td>Respiratory Muscle Endurance</td>
<td>RET = exhaustive normocapnic hyperpnoea RMT</td>
<td>McElvaney et al. 1989</td>
<td>Respiratory Muscle Endurance</td>
<td>2. time of sustained breathing against an inspiratory pressure load equivalent to 80% of C&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>Bousanna et al. 2001</td>
<td>Respiratory Muscle Endurance</td>
<td>RME = is the property of respiratory muscle that affords resistance to fatigue</td>
<td>Wirnsberger et al. 1997</td>
<td>Respiratory Muscle Endurance</td>
<td>RME = time (sec) that the maximum load (ascertained in an incremental test) could be tolerated</td>
</tr>
<tr>
<td>Supinski et al. 1985</td>
<td>Respiratory Muscle Endurance</td>
<td>Suggested that RME is determined in part by the balance between energy consumption and energy availability</td>
<td>Kochelin et al. 2005</td>
<td>Respiratory Muscle Endurance</td>
<td>RME = max time Tlim a subject is able to sustain a specific sub maximal muscle task</td>
</tr>
<tr>
<td>Nickerson &amp; Keens 1982</td>
<td>Ventilatory Muscle Endurance</td>
<td>Endurance is the property that affords resistance to fatigue</td>
<td>Chang et al. 2005</td>
<td>Inspiratory Muscle Endurance</td>
<td>Fatigue Resistance Index = FRI</td>
</tr>
<tr>
<td>Keens et al. 1977</td>
<td>Ventilatory Muscle Endurance</td>
<td>VMET = muscle endurance is correlate d with resistance to fatigue</td>
<td>Morrison et al. 1989 (A169)</td>
<td>Respiratory Muscle Endurance</td>
<td>RMEMSV = Maximal Sustainable ventilatory capacity is the highest ventilation that can be sustained for 15 min.</td>
</tr>
<tr>
<td>Forte et al. 1997</td>
<td>Ventilatory Muscle Endurance</td>
<td>Endurance of the Inspiratory muscles can be measured as the capacity to sustain intense breathing tasks</td>
<td>Bousanna et al. 2003</td>
<td>Respiratory Muscle Endurance</td>
<td>RME = corresponds to length of time resp' load can be sustained before fatigue develops sufficiently to cause task failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kerr &amp; Schultz 1996</td>
<td>Inspiratory Muscle Endurance</td>
<td>Endurance def' by length time load can be endured before process of fatigue develops sufficiently to cause task failure</td>
</tr>
</tbody>
</table>
**2.2.6 Design and Quality of Studies**

The sample sizes of participants varied widely ranging from 4 (Boutiller & Piko 1992) to 160 (Chen & Kuo 1989). In terms of methodological design, studies were found to be; cohort (N=81); matched control (n=16); healthy matched controls (n=11); or double blinded randomised control (n=2).

There were many examples of poor scientific rigor in articles identified in the review. Some studies were clear and frank about methodological issues associated with assessing respiratory muscle endurance, Martin et al (1986) described how ‘the major weakness of the study is the assessment of ventilatory muscle endurance’ primarily due to the arbitrary nature of their measure of endurance.

The most common examples of poor scientific rigor include; not describing the gender of subjects (Mador et al 2005; Koessler et al 2001; Nava et al 1992; Orenstein et al 1981); little or no detailed methodology of the technique used to assess endurance (Laghi et al 2005; Sonne & Davis 1982; Cimen et al 2002; Weiner et al 1993; Levine et al 1986); not clearly defining outcome measures (Wanke et al 1994; and Martin et al 1986); that while assuming that maximal ventilatory capacity is a measurement of RME (the accuracy of this assumption is discussed later in section 2.2.9), that this assumption is not stated in method or results sections (Sairikaya et al 2003; Belman & Mittman 1980; Forte et al 1997; Cimen et al 2003; Morgan et al 1987; Warren et al 1989); and poor reporting of results, such as not quantifying absolute figures returned and the use of graphs instead of tables (Boussana et al 2001; Holm et al 2004; Chatham et al (1996); Weiner et al 1998; Johnson et al 1998; O'Donnell et al 1998; Scardella et al 1993).

### 2.2.6.1 ‘The effect of inspiratory resistive training on exercise capacity in optimally treated patients with severe chronic airflow limitation’ - McKeon et al (1986).

A paper that stands out as a poor example and requires further appraisal is that of McKeon et al (1986) which is a study based around the use of an inspiratory training device. This study was designed to assess the effect of inspiratory resistive training on exercise capacity in patients with severe chronic airflow limitation. There is no mention of IME in the introduction, method or results sections of the article. It does not define what IME is, how it was measured or how it was seen to change. This makes the claim in the first sentence of the discussion all the more extraordinary:
‘There was no significant increase in maximum inspiratory pressure in the 10 trained subjects, but IME improved’.

The training protocol was based on breathing through a device with fixed orifices that could be made progressively smaller. In the discussion the authors then allude to an ability to ‘tolerate smaller apertures to be an indication of improved IME’. It is on this basis that ‘subjects in the study could be considered likely to have improved their IME’. It is clear that this study lacks any clear rationale for, or a definition of, endurance and the poor scientific standards of the article are further compounded by non-reporting of the subjects’ gender.

The way that this influences the development of future research can be seen in the resulting 7 citations this article received by subsequent authors of further original studies (Harver & Mahler 1989; Lake et al 1990; Guyatt et al 1992), systematic reviews and meta-analyses (Smith et al 1992; Pardy & Rochester 1992, Geddes et al 2005; Geddes et al 2008). This second review by Geddes et al (2008) prompted the author of this thesis to write a letter to the publishing editor outlining many of the points made already in this thesis, which was successfully accepted for publication (Powell & Williams 2009).

Geddes and co workers responded to the concerns raised surrounding the issues identified here within the topic of RME assessment (Geddes et 2009), stating that ‘many authors performing clinical research perceive these tests (of endurance as outlined in the review) to be estimates of RME’ (emphasis added). This didn’t really answer the concerns raised, indeed the use of the terms ‘perceive’ and ‘estimate’ actually reinforce the issues that are felt to be present in that there is no direct measurement of respiratory endurance. Geddes and co-workers did however agree that a standardised test protocol was needed for assessment of RME.

2.2.7 Inspiratory Muscle Training Studies

The premise that function of the respiratory muscles can be independently trained and adapted has driven a great deal of clinical and commercial interest, especially as breathing may be regarded as a form of muscular exercise (Rankin & Dempsey 1967). Although the lung airway and vascular structures seem to be resistant to the stimulus of physical training, as while it is not uncommon for elite endurance athletes to have large lung volumes and flow rates this is more likely due to why they are an elite athlete, than as a result of the training associated with it (Dempsey 2006).
Regardless, the notion that the endurance capabilities of patients with chest disease can be easily increased by relatively simple exercises that can be conducted without clinical supervision has been a focus for many in the respiratory field. However as has been set out up to this point there appears to be no common consensus on a definition of respiratory endurance, let alone any reliable non-invasive assessment technique. For respiratory training studies there appears to be no clear method to assess the efficacy of the outcome of any intervention in terms of respiratory endurance. Even though two double blind randomised control trials were identified in the review, such complex study design is of no use if the outcome measures applied do not represent the intended outcomes.

In all, forty-three articles identified were inspiratory muscle training studies and it was not unusual for these studies to use the same device and/or technique to measure respiratory endurance as that that was used for the training intervention (Mueller et al 2006; Mador et al 2005; Rassler et al 2007; Chatham et al 1996; Johnson et al 1996A; Klefbeck et al 2000; Ries et al 1988). This questions how much potential changes in endurance were due to true physiological change or because subjects became conditioned to the device in question due to the learning effect that accompanies all volitional tests of respiratory function (Eastwood et al 1998).

### 2.2.8 Different Methods of Assessing Respiratory/Inspiratory/Ventilatory Endurance

A range of different approaches to assessing the endurance of the respiratory system were identified (Fig 2.4), all of these represented maximal protocols that either resulted in fatigue (B, C1) or could only be maintained for a short period (A, C2). Apart from maximal ventilatory tests (detailed in section 2.2.9) these techniques use various forms of external loads to increase the rate of respiratory work to maintain adequate ventilation. These methods of endurance to external loads can be summarised as either flow resistive loads for example when using a fixed orifice, elastic loads, or threshold loads in which a finite pressure is required to allow flow to occur (ATS 2002A). Resistive threshold pressure loading (described in section 2.2.10) is the most commonly used technique, based on a device designed by Nickerson & Keens (1982) (Section 2.2.14.1).
Figure 2.4: Methods of Assessing Respiratory/Inspiratory/Ventilatory Endurance identified in review (number of trials); (A) Maximal Voluntary Ventilation – 25; (B) Incremental Test to fatigue - 42; (C1) Sustained test to fatigue – 34; (C2) Sustained test at highest possible load for set time - 18. (Note: some articles used more than one method).

2.2.9 Maximal Ventilatory Ventilation (MVV)

The goal of ventilatory endurance testing is to define the maximum ventilation capacity (L.min⁻¹), when over a short period ≤ 15sec this is described as Maximal Voluntary Ventilation (MVV). It is difficult for a truly maximal level of ventilation to be maintained beyond a short time and sustained ventilatory tests have been developed which use a percentage of a 15 second MVV test as a target ventilatory rate. This can be defined as Maximal Sustained Vital Capacity (MSVC) or Sustained Vital Capacity (SVC) can be for a period of up to 12-15 minutes (Levine et al 1992; Di Marco et al 1985).

MVV is the oldest method of measuring ventilatory and respiratory muscle endurance (Rochester 1988), and has been widely used as a test of ventilatory function (Freedman 1970) and breathing capacity. ATS (2002) describes this ventilatory test as ‘a measure of both inspiratory and expiratory muscle endurance’, undoubtedly due to the simplicity of the test and what it represents. It is though a somewhat ‘blunt instrument’ that should lead on to more specific tests in the presence of poor performance (McConnell 2007).
MVV gives a fatigue index of the respiratory muscles as the progressive decline in flow rate is due to muscle fatigue. Zocche et al (1960) considered that fatigue of the respiratory muscles was the main cause of attenuation of ventilatory capacity during sustained hyperventilation. By measuring the point of fatigue as already argued (Section 1.9) this represents the point when the endurance capability of the respiratory system fails and therefore it is incorrect to use it as an index of respiratory endurance. Additionally, a common occurrence was for studies to report MVV results and refer to this as a marker of endurance or not even make such a connection assuming that this is an accepted technique (Section 2.2.6).

MSVC that is assessed for significant periods is a more accurate picture of endurance as it does not result in fatigue or cessation of test. However maximal ventilation involves significant cooperation on behalf of a subject which is not in concurrence with the aims of this thesis. Further more ventilatory levels during maximal aerobic exercise rarely get close to levels of MVV. This would mean that it would be difficult to undertake a clinically relevant task that would elicit the same physiological response so the utility of the MSVC is questionable.

2.2.10 External Resistive Loading
As resistance is added to the flow of air during respiration, an increased inspiratory and expiratory effort is required to maintain adequate ventilation (Cain & Otis 1949). Resting breathing patterns can be altered to overcome this resistance and such strategies are successful. However when increased ventilation is required for example during physical exercise these cannot be used to compensate. Examples here are of the obstructed airways in chest disease and the use of purse lipped breathing and lung hyperinflation by patients.

To date all devices that used external resistive loading were constrained by the issue of a fixed orifice or load that could at best be adjusted between breaths. This meant that all these devices were constrained by the ability of a subject to alter their breathing pattern. The R_K device outlined subsequently (Section 3.1) is the first device that is able to continuously alter its internal diameter during a breath so that strategies to overcome the resistance are unsuccessful and subjects are required to increase their work of breathing or cease breathing through the device.
### 2.2.11 Threshold Pressure Loading

When an external mechanical load is applied to the airway opening, the respiratory muscle must generate an additional pressure to overcome the impedance of the load (ATS 2002^A). Threshold Pressure Loading (TPL) is based on the initial work of Nickerson & Keens (1982) and many commercial devices that are based on similar principles have been developed. The device consists of a plunger which must be moved to allow for air flow to take place. The resistance of the plunger can be controlled either by a metal spring or by adding weights. These are basic mechanical devices with few moving parts which make them easy to use and setup. As TPL often follows a maximal protocol an operator has to closely monitor the subject to ensure correct techniques i.e. maintain a seal around mouthpiece. While calibration of the resistive load is easy with weights, devices that use springs are more difficult to calibrate with inspiratory pressure manometers connected to the device.

As reviewed (Section 2.2.14.1) Nickerson & Keens (1982) originally outlined a sustained test, however the work of Martyn et al (1987) has now superseded this and all TPL studies now use incremental test protocols that result in fatigue. In patients with respiratory disease when fatigue may occur quickly discontinuous protocols have been developed when there are short rest periods in between the incremental stages of the trial (Larson et al 1999; Covey et al 2001). The outcome of these trials depending on the sophistication of the device used either use time taken for fatigue to occur, expressed as endurance time or if connected to a pressure manometer the inspiratory pressure needed to move the plunger at fatigue expressed as peak mouth pressure.

As has been previously discussed (Section 1.9) methods that result in fatigue do not represent endurance and therefore TPL protocols that result in fatigue cannot be used to measure respiratory endurance. However the ATS (2002^A) describe incremental TPL as the most useful method to assess respiratory endurance and it was found to be the most commonly used technique in this literature synthesis.

### 2.2.12 Controlling Breathing Pattern During the Respiratory Endurance Test

A wide variation exists in methods of controlling breathing, even within tests of respiratory endurance that use the same technique. With Incremental PTL previous studies have taken different approaches to breathing pattern. Specifically the variation in Respiratory Rate (\(f_R\)) and the time of inspiration (\(t_I\)) regards to the total breath time (\(t_{Tot}\)), expressed as \(t_I/t_{Tot}\).
These include not stating a $f_R$ or $t_{I/Tot}$ (Laghi et al. 2005), controlling both $f_R$ and $t_{I/Tot}$ (Koppers et al. 2006; Nava et al. 1992); allowing subjects to self-select $f_R$ but using a preselected $t_{I/Tot}$ (O'Kroy and Coast. 1993); and controlling $f_R$ while subjects freely select $t_{I/Tot}$ (Morrison et al. 1989). Attention should also be drawn to the preselected $t_{I/Tot}$’s that have been used, while they can vary, more often they are fixed at 0.5, not at a more ‘natural’ 0.4.

The reason for these differences is not apparent from any methods described, but is probably due to the availability of standard commercial (i.e. symmetrical) metronomes, those principally designed for musicians, rather than a belief that a $t_{I/Tot}$ of 0.5 reflects the most appropriate breathing pattern.

In terms of making any new method of respiratory endurance simpler to complete it would be more preferable to not have to control breathing rate, however this must be in context of the outcome of any test and the effect varying $f_R$ may have.

2.2.13 Does a Gold Standard Exist?

Hart et al (2002) describe their method as a reliable endurance test but this requires the insertion of a balloon catheter for measuring oesophageal pressure. This technique is seen as reliable as it measures changes in intrathoracic pressures which are seen as more accurate and representative of chest wall mechanics. However as previously described (Section 1.11) invasive testing is a highly specialised technique and carries with it an inherent risk. As such it is not suitable for use outside a laboratory without specialist equipment and trained staff. Furthermore this technique uses an incremental protocol which results in fatigue and as has been argued, fatigue is not equivalent to endurance.

Many different methods were identified in this synthesis and can be categorised into 4 main types (Section 2.2.8) yet very few of the papers identified in this review either used identical protocols or compared their techniques with other studies. This therefore makes it difficult for comparisons to take place between techniques.

Geddes et al (2009) describe how it would appear that respiratory muscle tests are selected based on whether they can estimate the desired outcome, are straightforward to perform, are not unduly challenging, and are accessible, reliable, and preferably non-invasive. That is, tailored to the particular demands of a research question, not because of a clear rationale why it would be the best measure of respiratory endurance. As such it is difficult to see how a
comparison with a gold standard and techniques developed within this thesis could take place.

2.2.14 Key Historical Articles

There are three studies that were frequently referred to by other articles in this synthesis. The most cited was Nickerson & Keens (1982) (cited 54 times), this article fulfilled inclusion/exclusion criteria and appears in this synthesis. Also cited frequently (n=30) was Martyn et al (1987) who built on the work of Nickerson & Keens, however none of the search terms for this review appear in the title or abstract with the authors referring to ventilatory muscle performance and not mentioning endurance and it is therefore not included. Both these articles utilised a TPL device. The study by Leith and Bradley (1976) (cited by 33 articles) refers to maximal ventilatory flow measurement as an index of endurance.

For such widely cited articles that a great deal of subsequent research studies were based upon, it is surprising that only small cohorts of subjects were studied; Nickerson & Keens - 7 (wide age range: 5-75 years); Leith & Bradley -12 (healthy adults, age: 20-40 years); Martyns et al - 14 (healthy adults age: 21-44 years).

Furthermore in terms of making a clear definition of endurance Nickerson & Keens, and Leith and Bradley clearly do so; ‘Endurance is the property of a muscle that affords resistance to fatigue’; and ‘(Ventilatory Muscle) endurance is the capacity for sustaining high levels of ventilation for relatively long periods’ respectively. Martyns et al while not clearly defining respiratory endurance described the innate difficulty and tests that had been previously used; ‘measurements of (ventilatory muscle) endurance are more difficult and two general types of test have been used; voluntary hyperpnoea and inspiratory threshold loading’.

2.2.14.1 ‘Measuring ventilatory muscle endurance in humans as sustainable inspiratory pressure’ – Nickerson & Keens, 1982

Nickerson & Keens constructed a plunger device (Fig 2.5) that has been widely used and replicated in the many articles that cited them. Their protocol set the plunger device at a proportion of MIP by the addition of weights to the plunger. These weights would be adjusted until the maximum load that could be sustained for 10 minutes is identified. The inspiratory pressure needed to overcome the weighted plunger is used as the test outcome and is referred to as the sustainable inspiratory pressure (SIP). This technique relies on correctly measured MIP which as described previously would require up to 20 separate MIP measurements to
ensure that a maximum value had been achieved. While this may work well in the laboratory, such an involved protocol may not transfer that well into a clinical or home setting. Interestingly Nickerson & Keens identified a 10% increase in MIP and SIP at a two week retest. This raises possible issues of learning with this form of respiratory measurement?

Nickerson & Keens identified that endurance cannot be assessed by strength and that endurance is the property of a muscle that affords resistance to fatigue. They identified previous techniques which used the highest volume of isocapnic hypopnoea that could be sustained for a given time. Such techniques dependence on flow rate made it difficult to compare between health and disease preventing it from being easily used and interpreted clinically. The non-fatiguing protocol they described, although requiring maximal subject cooperation was closer to a test of endurance than maximal fatiguing tests.

In conclusion more so than the technique they describe, the point that Nickerson & Keens make about endurance being dichotomous with fatigue is probably their greatest contribution to the field of respiratory endurance measurement. Unfortunately it would appear that this has since been ignored by subsequent researchers.

2.2.14.2 ‘Measurement of inspiratory muscle performance with incremental threshold loading’ - Martyns et al 1987

Martyns et al. were concerned with the learning effect that was identified with Nickerson & Keens’s method. They showed that using the Nickerson & Keens protocol and device, SIP was increased by 25% when measured twice. Therefore they chose to use incremental loads and ‘developed a test similar to a progressive test’. Outcome was defined as peak mouth pressure at the greatest load achieved (PmPeak). In effect Martyns et al used the device of Nickerson & Keens but applied a totally different protocol. As argued previously an incremental test resulting in fatigue does not measure endurance, and Martyns et al seem to ultimately acknowledge this by referring to how their incremental technique is a simple assessment of ventilatory muscle performance rather than endurance.

Interestingly Martyns et al identify how subjects vary their pattern of breathing and that breathing strategies influence the measurement of SIP. They contend that by incrementing a load subjects were able to vary their breathing pattern to maximise their performance in the test. They do not say whether this could also have a negative effect on test performance.
In conclusion this paper was responsible for the development of an incremental (fatiguing) protocol and many subsequent studies make clear how they use a modified Nickerson & Keens protocol which directly or indirectly relates to the work of Martyns et al.

Figure 2.5: Illustration of Nickerson & Keens (1982) weighted plunger device

2.2.14.3 ‘Ventilatory, muscle strength and endurance training’ – Leith and Bradley (1976)

Leith & Bradley used a standard measurement (15 sec MVV) as their test of endurance. As stated previously MVV has been widely used as a marker of ventilatory function (Section 2.2.9). Yet it appears from articles that Leith & Bradley cite that it is only around the time their article was published that MVV and endurance come together as a common theme. Of the articles they (Leith & Bradley) cite only Tenney and Reese (1968) also express their findings in terms of endurance time. Indeed many articles that Leith & Bradley cite discuss maximal ventilatory tests within a fatigue context.
As have been described with other training studies (Section 2.2.7) they developed a piece of equipment for respiratory training (Fig 2.6) that was also used to assess endurance which raises issues of training effect on the endurance measurement. They measured (ventilatory muscle) endurance as time to exhaustion during partial re-breathing in a system which permitted regulation of inspired \( O_2 \) and \( CO_2 \) levels and which provided a ventilatory target (although it is not clear from their method what this target was). They also describe the need for repeated trials so the subjects could learn the test, suggesting that substantial amounts of training would be needed to ensure a repeatable/reproducible test outcome.

With the large number of citations for this article and lack of evident use of endurance terminology before it, it is not unreasonable to speculate that it is the starting point for the use of maximal ventilatory tests as indexes of respiratory or more commonly ventilatory endurance (see Section 2.2.9). Leith & Bradley describe how previous studies have described and measured (ventilatory muscle) endurance as the capacity for sustaining high levels of ventilation for relatively long periods. However as they describe a protocol resulting in exhaustion this cannot be used to represent endurance.

![Diagram](image)

**Fig. 2.** Partial rebreathing system incorporating a bag-in-box to permit measurement of oxygen consumption during rebreathing hyperpnea at known levels.

**Fig 2.6: Leith & Bradley (1976) Endurance Training/Measurement Device**
2.2.15 Research Questions to Answer

1). What is RME?
Research muscle endurance represents the ability of the respiratory muscles to continue to drive the internal pressure gradients within the lung needed to maintain ventilation indefinitely. In practical terms when assessing the respiratory system non-invasively, the action of the respiratory muscles cannot be isolated from the other components of the respiratory system, therefore in this context the term ‘muscle’ should be removed from any definition.

2). How has respiratory endurance been defined?
Currently there is no established definition of respiratory endurance, and not all studies clearly state one. In those that do any definition is based on the methodology rather than an underlying physiological parameter. Furthermore endurance is often framed with a fatigue context. Fatigue is difficult to define but certainly involves a large psychological component, probably a reaction to the unpleasant sensation of excessive ventilation (Shephard 1966). Furthermore fatigue represents the point at which endurance fails or ends. The two terms, fatigue and endurance, are not synonymous.

While a measure of fatigue provides valuable information about an individual’s maximum capacity, it does not measure the clinically important ability of the respiratory system to endure sub-maximal loads such as those experienced during the physical activities of daily life. It is the consideration of the difference between maximal diagnostic testing and sub-maximal functionality testing of the respiratory system that is pertinent, as both are important and valid. A definition that regards the respiratory system as a whole would be more accurate and therefore ‘Respiratory System Endurance’ or ‘Respiratory Endurance’ would be a more preferable term.

3). How has respiratory endurance been measured?
Many techniques have aimed to assess respiratory endurance but cannot be said to do either due to their inability to correctly define endurance or use of a protocol that results in fatigue. Techniques that use a sub-maximal, constant state testing in methodological terms, would be the most applicable when assessing respiratory endurance. The methods identified in this review have been used in a wide range of subject groups including paediatrics, elderly, chest disease, muscle wasting disease, during exercise and at rest in healthy controls. Mostly they
have been used in small studies within clinical or laboratory environments and none have been used to test respiratory endurance within the home environment for example. Often these methods were used to assess the outcome of respiratory training studies although due to their intimate connection with the training intervention, it would be difficult to assess the efficacy of an outcome due to the potential for learning effect.

2.2.16 Proposals for Future Research Within Respiratory Endurance Testing

From the syntheses of the existing research the following areas for future research are proposed.

1) What form should a sub-maximal protocol follow?
   - Paced versus unpaced breathing
   - Load intensity
   - t/tTot ratio
   - Metronomic control of breathing pattern

2) How repeatable and reliable is any such protocol/technique?

3) What effect does physical exercise have on the outcomes of the protocol?

4) Can the protocol be used to distinguish between health and disease?
2.3 Tidal Breathing Profile Analysis - Developing the Research Question

The ability to measure respiratory function during tidal breathing regardless of the age or respiratory state of a participant would be particularly advantageous especially in those individuals when it is difficult or not possible to perform forced expiratory manoeuvres (Lodrup-Carlsen. 2000). For example as COPD severity increases it becomes hard for patients to cooperate as they get older, suffer from more co-morbidities and experience more exacerbations of their disease symptoms (Soriano & Miravitlles 2009).

As such there has been interest in the development of techniques that use a passive non-volitional protocol which have mainly focussed on the shape of the expiratory flow curve as an index of airway obstruction. Colsanti et al (2004) have taken this technique further and developed algorithms that can be used to predict airway obstruction incorporating parameters derived from expiratory airflow curves. This technique is described in detail later (Section 3.2), and has been reviewed in editorials (Bates et al 2000) but has not been studied by others. Therefore it is only possible to review existing studies that have studied parameters derived from the resting tidal expiratory airflow curve most notably PTEF and the time taken to achieve this ($t_{\text{PTEF}}$).

2.3.1 Redefinition of the Research Question.

To facilitate the synthesis of the existing literature in the context of developing a synthesis rather than a simple review of the literature it was necessary to adapt the original research question to meet the needs outlined in section 2.1. The original question needed to be adapted to become more specific and to identify its key components and definable ways of answering these;

1) In terms of PTEF what is the best technique or protocol to use to accurately collect this parameter?
2) What type of participants has it been collected in and how well was this tolerated/undertaken?
3) Can differences be observed using resting tidal profiles in groups with different lung function?
4) How reliable a technique is it to accurately represent airway obstruction?
2.3.2 Formulation of Search Strategy

1. Search term
   Peak Tidal Expiratory Flow – ‘PTEF’
   time to Peak Tidal Expiratory Flow- ‘tPTEF’

2. Format of literature
   Original research studies published in peer reviewed academic journals and textbooks

3. Location of sources
   Relevant academic journals (see Section 2.2.3)

4. Selection criteria
   Articles were identified by the appearance of the search term in either the article title or the body of any abstract

5. Inclusion/Exclusion criteria
   Described the measurement of PTEF / tPTEF
   Related to human physiology
   In English
   Full Article, not personal communication or conference abstract
   Available to reviewer as either paper or electronic copy

6. Other Sources
   Journals that yielded articles identified in search and other Respiratory, Physiology, and Sport & Exercise journals were regularly appraised (see Section 2.4).

Figure 2.7: TBPA Search Strategy

2.3.3 Results of Search

The search strategy yielded thirty-two articles consisting of twenty-nine original articles and two reviews and one methods paper. The relevant academic journals regularly appraised as part of the respiratory endurance review (Section 2.2.2) were also regularly checked for relevant articles. Each article was critically appraised for; terms and definitions used; study design; sample size; subject group; assessment method & protocol; and assessment results. The results were then tabulated (Appendix 2.3).
2.3.4 Range of Academic Journal and Year of Publication

Articles appeared in a range of journals although were mainly concentrated on specialist adult and paediatric respiratory journals. Two journals responsible for publishing the most articles were the Paediatric Pulmonology (n=10) and the European Respiratory Journal (n=8). Despite the chronological ages of research databases used (Section 2.2.4) the earliest paper that fulfilled search criteria was 1994. This is perhaps driven by the computing power necessary to process the large amounts of data generated using this technique into the outcome parameters required especially over prolonged epochs.

2.3.5 Parameter and Indices Used

The most common parameter reported was $t_{\text{PTEF}}$ (in 18/23 articles) commonly expressed as a proportion of $t_E$ ($t_{\text{PTEF}}/t_E$) representing the mathematical expression of the time and volume needed to reach PTEF (See section 3.2)). Morris et al (1998) used $T_{\text{rs}}$, the gradient of volume/flow which they indicated was more closely associated with airway resistance, although this technique would require measuring airway resistance (Section 3.4.3) and would require a more involved level of testing.

2.3.6 Device Used

Most studies used a pneumotach to measure flow profile although later studies have used respiratory inductance plethysmography - RIP (Stick et al 1996. Manczur et al 1999; Black et al 2004) which utilises belts around the chest and abdomen to indirectly assess Tidal Flow loops (See review by Wolf & Arnold 2005). This is not a direct measure of flow, as it uses changes in volume to derive flow. Manczur et al (1999) found that while both methods could be used to measure $t_{\text{PTEF}}/t_E$ the results were significantly different, although RIP was better tolerated.

2.3.7 Sample Rate and Sample Time/Length

Sampling rate was only stated in 11 of the studies and was seen to range from 80hz to 256hz. Bates et al 2000 in an ATS/ERS standards paper states that when using resting tidal parameters such as $t_{\text{PTEF}}/t_E$, greater resolution is needed and therefore rates of ≥200hz are recommended.

Sample length and time varied considerably between studies. The minimum used was 4 tidal breathing flow volume (TBFV) loops although the length of sample these were taken from varied from 8 (Devulapalli et al 2004; Lodrup-Carlsen et al 1999; Haland et al 2007), to 16 breaths (Totapally et al 2002). Other studies used breath sample sizes of 10 (Greenough et al 1998$^A$);20 (Ranganathan et al 2003) and 25 breaths (Yuksel et al 1996).
Time was also used for sample length and this varied from 20 seconds (Ueda et al 1999); 30-60 seconds (Habib et al 2003; Dezateux et al 1994); 60 seconds (Dotta et al 2007); 80 seconds (Morris et al 2004); and 2 minutes (Williams et al 2000). 5 studies did not describe the sampling time or length used.

Using shorter sample times relies on the operator to identify the TBFV loops that are used for analysis and therefore brings bias to any measurement. By sampling a longer period and taking the average of any parameters and filtering any outliers this can remove such bias (See van der Ent et al 1996 for discussion of this). Shorter periods may be poorer in terms of getting truly resting breathing patterns, however longer epochs may not be possible in some subjects.

2.3.8 Sedation of Study Participants

There are issues with sedating acutely or severely ill respiratory patients (Table 2.4) and the sedation of healthy children in many European countries (for example Norway) for research purposes is not allowed for ethical reasons (Lodrup-Carlsen 2000). However collection of undisturbed tidal breathing is a complex undertaking as the process of measurement can influence the pattern of breathing (Bates et al 2000) and sedation has been used to elicit a rested response from infants tested. In this synthesis 8 of the 21 studies of infants used sedation in their protocol, usually in children <12 months although Deeronjanawong et al (2005) report sedating children up to the age of 5 years. The use of sedation in a protocol would preclude any study in a non-clinical environment.
Table 2.4: Guidelines for Sedation of Infants When Measuring Tidal Breathing
(adapted from Gaultier 1995)

1. Contraindication for sedation - known upper airway obstruction

2. High risk infant groups:
   - a) preterm and full-term neonates (≤44 weeks post-conception age) even when healthy;
   - b) infants presenting a history of acute life-threatening events;
   - c) infants at increased risk of upper airway obstruction;
   - d) infants with known respiratory embarrassment;
   - e) infants with hepatic, renal, or cardiac disorders. High risk infants must be monitored (oxygen saturation, heart rate) after sedation. Overnight hospitalisation may need to be arranged for infants who are clinically unstable.

3. Sedate with caution - wheezy infant

4. Resonation should be avoided, the total dose of chloral hydrate should not exceed 120 mg·kg⁻¹ (and dose equivalents for related drugs, triclofos sodium)

5. Always advise parents of possible unsteadiness in infants post sedation

2.3.9 Research Questions to Answer

1). In terms of t_PTEF what is the best technique or protocol to use to accurately collect this parameter?

Pneumotachs appear to be the simplest method to collect tidal breathing data. Shorter sample times involve a tester to select the ‘best’ curves for analysis which may bring in certain levels of error. This would appear to be removed by using longer sampling times and automatic, non human, selection of flow curves for analysis. To adequately define all points of tidal flow especially at higher f_R a sample frequency of at least 200hz should be used.

2). What type of participants has it been collected in and how well was this tolerated/undertaken?

The use of resting tidal expiratory flow profiles have mainly been used in very young children who are not capable of standard lung function measurement. The only studies into older subjects were those conducted by Williams and colleagues. In the chronologically young patient groups, subjects were often sedated which would make the tests not applicable outside a clinical setting. The use of resting tidal breathing profile’s in older patient groups with respiratory disease warrants further investigation.
3). What differences were found between groups with different stages of lung disease/impaired respiratory function?

In studies that compared healthy controls with clinical groups that had some form of changed airway function either from disease, obstruction or the use of bronchodilators (n=12), 8 studies found significant differences in $t_{\text{PTEF}}/t_E$. Furthermore $t_{\text{PTEF}}/t_E$ was found to vary with ethnicity (Stocks et al 1997), be lower in children exposed to tobacco smoke inutero (Hoo et al 1998; Stick et al 1996; Ueda et al 1999) and was found to be lower in children who went on to become wheezy or asthmatic (Yuksel et al 1996; Dezatuex et al 1994).

4). How reliable a technique is it to accurately represent airway obstruction?

The potentially most troublesome aspect of tidal breath analysis from the computational point of view is the identification of the beginning and end of inspiration (Bates et al 2000) although this can be made easier with high enough sampling rates. Establishing a truly resting profile is the main aim of any protocol and this should be established after a period of quiet tidal breathing. It is unclear whether this can be achieved within a few breaths and may take a longer period of time (>2min) to be achieved. The reliability and repeatability of such measurements in health and disease requires further investigation.

2.3.10 Proposals for Future Research Within Measurement of TBPA

Resting tidal flow/volume measurements may be important supplementary tools in the investigation of respiratory disease in both research and clinical work (Lodrup-Carlsen 2000) as this synthesis has identified. More work is needed however on their use and the following areas for future research are proposed.

1) How repeatable and reliable is any such protocol/technique?
2) Can such protocol be used to adequately distinguish between health and disease?
2.4 Conclusions to Literature Review

In Summary……..
In this chapter I identified, located, retrieved and synthesised 142 research papers developing research questions for the thesis. The issues identified in the synthesis of respiratory endurance led to letter to the editor of the Journal of Respiratory Medicine being published.

1. The Participant
   - Existing tests of respiratory endurance often require participants to continue to fatigue.
   - TBPA has been used mainly in younger children due to the difficulty in them completing standard lung function tests.

2. The Test
   - Many of the studies identified have confused endurance with fatigue and no standard definition of endurance exists or a protocol to measure it.
   - TBPA has been used to detect change between health and disease although it is not as sensitive a measure as standard lung function tests.

Reliable tests of RME have been difficult to establish (Hart et al 2002) and the reasons for this have been explored within this research synthesis. It has been shown that there is some confusion within the literature about the exact nature of respiratory endurance and what it exactly entails. While many studies and reviews believe endurance and fatigue to be synonymous terms that can be used interchangeably this has been shown to be an incorrect assumption. Steady state sub-maximal tests of the respiratory system would appear to be the most applicable way of assessing respiratory endurance.

Resting tidal airflow measurements may be important supplementary tools in both research subjects and clinical patients who cannot cooperate with more conventional lung function measurements (Lodrup-Carlsen 2000). However they do not exist without some issues that must be addressed when using them, primarily that resting tidal airflow measurements are not as sensitive as spirometry. Although a simple tool to apply and as it is non-invasive and requires no cooperation from a participant, it cannot be used to reveal the severity or the presence of airflow obstruction with complete reliability (Bates 1998). However it could have uses in hard to test populations and situations. When used outside the laboratory, with airway
obstruction already confirmed with spirometry, resting tidal airflow measurements could be used to monitor lung function over time in the home or at work.

With both techniques the removal of significant effort on behalf of a participant means that they would be easier to undertake for the groups that find respiratory testing difficult and would also be simpler to apply. However this should be under the proviso that they may not be as sensitive as existing methods of assessing lung function.
Chapter 3 - Materials and Methods

3.0 Introduction and Overview

This chapter details the techniques and methods used during the studies described within this thesis. It begins by detailing how a new technique to assess respiratory system endurance, using the MicroRMA, was developed. It then gives detailed instruction in the use of Tidal Breathing Profile Analysis (TBPA) to predict FEV$_1$. The development of a Paced Breathing Metronome is then described before concluding with a description of standard lung function and exercise tests used later in this thesis.

3.1 Constant Resistance Device: Operation, Development and Outcomes

The MicroRMA\textsuperscript{1} is a commercially available device manufactured by Micro Medical Ltd (now Cardinal Health, USA). It is a USB driven device with proprietary software that can be operated by laptop or desktop computer. It is CE marked and is therefore safe to use for human testing. The work of this thesis details some of the early work with this device and its development. Currently no standard published protocol exists for assessing respiratory function with this device.

The MicroRMA has UK and EU patent applications (2 420 077 and 1 397 994 A1 respectively: Appendix 3.1) which describe the mechanics of the device in detail. The device consists of a flow sensor head and a SenSym SDX differential pressure sensor around the variable resistance tube (Fig 3.1). As the subject breathes through the MicroRMA probe, the flow and differential pressure are sampled every 100Hz. To

\textsuperscript{1} Within this thesis the MicroRMA is also referred to as the R$_K$ device
maintain a constant resistance ($R_K$) irrespective of flow the RMA software alters the internal orifice diameter of the breathing tube which transverses the flow probe (Fig 3.1). By either increasing or decreasing size of the aperture every $100^{th}$ of a second, $R_K$ load can be maintained at or close to the target resistance during the majority of each breath even at low flow rates. At a flow rate of 1 L.min$^{-1}$ through the MicroRMA results in a resistance of 0.14 kPa.L.sec$^{-1}$ (Fig 3.2).

Within the UK patent application the device is described as an ‘apparatus for determining respiratory muscle endurance of a person’. However the concept of endurance assessment is suggested to be a progressive test to fatigue, which results in endurance time. As has been argued previously (Section 1.9) such a test does not represent endurance of the respiratory system. However the ability of this device to 1) maintain resistive load independent of air flow, therefore reducing the ability of a subject to modify their breathing strategy during testing; and 2) easily record and integrate pressure and flow data with time allowing the work to be calculated (Section 1.12) suggests that this device warrants further investigation.

Figure 3.1: Internal Assembly of MicroRMA Device (from EU Patent): 48 = mouth piece; arrows are the direction of airflow; 44 = variable orifice.
3.1.2 Operation of Device

The appearance of the screen interface is outlined below. In simple terms an operator selects a $R_k$ load that they wish a subject to breathe against. The $R_k$ device is able to create $R_k$ loads up to 20 kPa.L.sec$^{-1}$ although in practice such a level of resistance would be impractical for use with human testing. The software allows the $R_k$ load to be altered in 20 increments for an indefinite period. The period of time is expressed in breath cycles. For example:

Subject A protocol
- 100 breaths @ 1.0 kPa.L.sec$^{-1}$;

Subject B protocol
- 100 breaths 25 breaths @ 0.25 kPa.L.sec$^{-1}$
  25 breaths @ 0.50 kPa.L.sec$^{-1}$
  25 breaths @ 0.75 kPa.L.sec$^{-1}$
  25 breaths @ 1.0 kPa.L.sec$^{-1}$. 

Figure 3.2: Inherent Resistance Developed by MicroRMA (manufacturer supplied)
As will be described later study participants were able to use this device in a variety of exercise modalities such as walking and cycling, and also whilst seated.

3.1.3 Why Choose a 6-minute Endurance Trial?

When developing techniques to assess respiratory endurance, a constant rather than incremental protocol would appear to be the best method to use when developing protocols to assess endurance (Section: 1.10; 2.4). However, the majority of existing techniques which aim to assess respiratory endurance use maximal and/or incremental protocols (Section 2.2.8). It is therefore necessary to look into another field where constant sub-maximal tests of endurance are widely used, for example human exercise testing.

Many tests that have been developed to assess human exercise endurance expressed as \( \dot{V}O_2 \) max (ACSM 2000; Wasserman et al 1999) to assess maximal oxygen uptake (see Section 3.5.1 below). Alongside such tests of maximal exercise capacity, sub-maximal tests have been developed that are used to assess physical exercise capacity and to predict maximal performance. These tests have been developed to use with specific populations such as individuals with chronic disease or for whom maximal testing is inappropriate. They have also been developed for situations when sophisticated equipment and trained staff are not available.

The most obvious sub-maximal exercise test for comparison is the 6-minute walk test, 6MWT. (ATS 2002). This test of functional exercise endurance is widely used in the clinical respiratory environment in patients with cardio-respiratory disease (see Section 3.5.3). Other sub-maximal exercise tests also exist such as the Astrand Rhyming Cycle Protocol (Section 3.52 - Astrand & Rhyming 1954). This is a single stage 6-minute cycle protocol that uses the relationship between HR and \( \dot{V}O_2 \) uptake to predict \( \dot{V}O_2 \) max.

A 6-minute sub-maximal protocol has several benefits over maximal testing principally by the removal of subjective motivation to complete the test. Establishing a definitive end-point gives the subject a target to achieve rather than having to work towards an unknown designated maximal point and the subject having to judge when they are exhausted. Noakes (2008) argues that in relation to maximal exercise testing
this is important, as accurate knowledge of the exercise duration optimises exercise performance. The goal of this strategy is to complete an activity without homeostatic failure or the development of a ‘‘limiting’’ muscle fatigue. Additionally by using a 6-minute, constant, sub-maximal protocol, subjects can achieve a steady-state level of ventilation and therefore steady state work rate. When given a constant stressor to preserve homeostasis the body adopts the most efficient manner to overcome that stressor. By assessing and measuring these adaptations an index of endurance capability should be suggested. With regards to respiratory testing this would represent a much better test of endurance than existing maximal techniques.

The few respiratory endurance protocols identified in the review of the literature (Section 2.2.8) that have used constant workloads for set time periods are those which use; 1) Maximal Sustained Ventilatory Capacity (MVV), varying from 10-minutes (Fairban et al. 1991. McConnell et al. 2003), 12-minutes (Levine et al.1992), 15-minutes (Belman & Kendregan 1982), to 150-minutes (Martin et al.1982^3); 2) Maximum % of MIP, for 10-minutes (Chen et al.1985. Nickerson & Keens 1982); or 3) Breathing through the smallest fixed orifice for 10-minutes (Ries et al. 1988). All of these studies use periods of time greater than 6-minutes. These long-duration respiratory endurance studies aim to assess maximal performance over time, even though they did not require the participant to finish the test because of fatigue. Given the conceptualisation that endurance can only be represented by achieving a constant sub-maximal steady state, this would suggest that a shorter duration trial as has been outlined would be more applicable.

3.1.3.2 The 6-minute Protocol
All subjects gave written informed consent and completed a study relevant health screening questionnaire before taking part. For all trials each subject held the \( R_K \) device (Section 3.1) while breathing through a mouthpiece and bacterial filter placed in series. All subjects wore nose clips and had no prior experience of breathing through the device.

When a participant indicated they were ready to begin they were asked to breathe through the \( R_K \) device until instructed to stop. The trial ended after six minutes or prematurely if the subject gave up or failed to maintain a tight seal around the mouthpiece to prevent air leakage. Participants had at least ten minutes rest between
each trial or until they felt ready to continue, during which they were given the opportunity to rest and drink water. Participants were given no instruction during any of these trials on their expected $f_R$ or $t_I/t_{Tot}$ ratio and therefore maintained a self-paced or volitional rate throughout. Additionally no verbal encouragement was given throughout the trials.

All studies were approved by the Faculty of Health, Sport and Science ethics committee and where applicable and relevant, local NHS Trust Research departments, and Local Regional Ethics Committees.

3.1.4 Development of Software

One of the key aspects or benefits of working closely with an industrial partner, in this case Micro Medical Ltd, was to adapt the MicroRMA’s software to increase the functionality of the device.

3.1.4.1 MicroRMA Software Version 1.01

This was a Microsoft Windows based software allowing control over a USB driven device, the MicroRMA. The software consists of variety of data formats and output styles including tables and graphs (Fig 3.3). It is a sophisticated package that allows detailed input of patient parameters, gender, height & weight, date of birth, smoking status, ethnic origin and the capacity to assign a unique alpha-numeric patient identification (Fig 3.4).

As described in Section 3.1.2 the $R_K$ load is set in kPa.L.sec$^{-1}$ over breath cycles as opposed to time. The $R_K$ device allows up to twenty alterations in applied resistive load with indefinite breath cycles per level (Fig 3.5). The software automatically provides biological feedback allowing the subject to maintain a set breathing rate during trial (central red line; Fig 3.6), between set limits. A number of graphs and tables can be used to represent outcomes of particular trial (Fig 3.7). The facility also exists to export raw data as a comma-separated value file, consisting of time, pressure and flow data sampled at every 100 Hz (Figure 3.8).
Figure 3.3: Main User Screen

Figure 3.4: Adding a Patient

Figure 3.5: Applied Resistance per Breath Cycle

Figure 3.6: Bio-Feedback
3.1.4.2 First Stage Software Development.

On initial use a number of issues with the initial version of the software interface were identified. These included;

Issue 1) Data Output.

The software presented test results as cumulative values in both tabular and graphical form. However, it also allowed direct export of the raw data, although it should be noted that while the device samples at 100 Hz, (once every 10 milliseconds), the raw data recorded an average of ten such cycles and therefore represents a mean over 100 milliseconds. Despite the operation of the device based on setting the $R_K$ load per breath cycle, there was no facility either in the on-screen form or raw data export to express the outcomes of a trial in a similar per breath fashion.
Resulting from this issue; 1) The exported raw data is now additionally expressed in per breath terms; and 2) a new graph option of Energy per Breath has been added.

Issue 2) Age Limit.
The software allowed a subject's date of birth to be entered as the day of the test i.e. that the subject was 1 day old.

Resulting from this issue; 1) A date different from the day of test date had to be entered under subject details. However the range was set from 1 -150 years which indicates a lack of clinical relevance or experience on behalf of the software developer(s).

Issue 3) Start of Test.
With the software the test began as soon as the operator selected the start test option with no relation to the point in the respiratory cycle the subject was currently at. Therefore, the length of the first breath cycle was often markedly shorter than later breaths. This was important due to the way that applied load was set per breath rather than by time.

Resulting from this issue; 1) a breathing cycle now begins on inspiration and ends on expiration; and 2) when the test is started it only begins on a subject’s next inspiration.

Issue 4) Sound Incentive.
The software incorporated an audible beep on a subject’s inspiration. The pacing of this beep therefore matched a subject’s respiratory rate and was not an instructional metronomic function in any way which led to significant confusion, particularly when a metronome was used to pace breathing.

Resulting from this issue; 1) this function was removed.

Issue 5) Battery Storage.
The MicroRMA device while host powered through a USB port also has an intrinsic battery that needs to maintain a level of charge for operation. With frequent use
battery charging occurs and low charge is not an issue. However with prolonged
periods of non-use the battery can run down and needs a period of time before
operation can commence when initially connected. An indicator of battery charge
level would be a useful tool for an operator, either as a software option or built into
the device.

Resulting from this issue; 1) due to the capital investment and work needed to
redesign the hardware of the device this adaptation was not undertaken.

3.1.4.3 Second Stage Development

Further use of the device led to the identification of further issues. These included;

Issue 1) Set Zero Flow Reminder.
Before each test the device guidelines to zero the flow reading, and there is an option
to do this. However as with all tests, operator error can mean that this is not always
undertaken.

Resulting from this issue; 1) A prompt before each test was incorporated. However
the manufacturer commented that some medical professionals may find this irritating
and as a compromise, an option was created where it could be selected that an
operator was prompted before each test to zero the device.

Issue 2) Metronome Timings.
As is discussed elsewhere a need for a metronome with the ability to pace both
inspiration and expiration was identified (Section 2.2.12).

Resulting from this issue; 1) A new metronome was incorporated within the program
that allowed the length of inspiration and expiration within a breath to be predefined.
Unfortunately on testing the integration of this metronome within the software
package was found to be unreliable. This drove the separate development of a paced
breathing metronome described below (Section 3.3).

3.1.5 Calculation of Test Outcomes

While it was possible to develop the controlling software it was not possible to adapt
the software in terms of outcome measures. The MicroRMA software displays
graphical outcomes (Fig 3.3) however these aren’t suitable for research use as they
give no quantifiable data and cannot be accurately controlled to end a trial precisely. Therefore for each trial undertaken the raw data for each test was exported as a CSV file, this gave continuous flow (litres per second) and pressure (cmH$_2$O) data sampled at 100 Hz. Pressure data was converted to kPa in post analysis.

Within a data manipulation package (Microsoft Excel), macros (a sequence of computing instructions as a single program statement) were created that were used to calculate the following parameters from this raw data. Primarily this was so that each raw parameter (flow, pressure and time) could be converted from being expressed every 10 milliseconds to every breath. Change from negative to positive pressure was used to define point of inspiration/expiration. From these data all further study parameters were calculated.

3.1.5.1 Breaths
Expressed as a respiratory rate and the cumulative number of breaths in a trial ($f_R$).

3.1.5.2 Time – t (seconds)
Expressed as Total breath time ($t_{Tot}$), Time of inspiration ($t_I$), Time of expiration ($t_E$), and the ratio between time of inspiration and total breath time was calculated ($t_I/t_{Tot}$) (Fig 3.9). Total time to trial end ($t_{END}$) was calculated by cumulatively summing individual breath times in each 6-minute trial identified by the nearest whole breath to 360 seconds which was taken as the trial end-point.

3.1.5.3 Volume – V(Litres)
Flow data integrated with time gives volume (Fig 3.10). The volume of air inspired was expressed per breath as inspired tidal volume ($V_T$) and per minute as minute ventilation ($\dot{V}_E$). Respiratory drive was expressed as inspired tidal volume divided by time of inspiration ($V_T/t_I$).
**Figure 3.9:** Time Parameters Calculated per Breath. Time of inspiration (tᵢ), time of expiration (tₑ) and the total breath time (t_{Tot}) in seconds. Note: representation of healthy breath.

**Figure 3.10:** Integration of Inspiratory Flow (L) With Inspiratory Time (sec) to Produce Inspiratory Volume per Breath – Tidal Volume (V_{TI}(L)) Note: representation of healthy breath.
3.1.5.4 Energy - W (Joules)

Energy was calculated by integrating time, volume and pressure data (Fig 3.11). Defining the point of inspiration/expiration during each breath allowed the energy (J) used during the inspiratory (W_I) and expiratory phases (W_E) of tidal breathing to be calculated.

3.1.5.5 Work of Breathing at the Mouth - W_{rs}^{mouth} (J.L)

Work of Breathing at the mouth (Section 1.10) was calculated by integrating the inspired volume per breath (V_{TI}) and energy used per breath (W_I or W_E), and expressed as work of breathing at the mouth on inspiration (InW_{rs}^{mouth} J.L) or expiration (ExW_{rs}^{mouth} J.L).

Figure 3.11: Energy – W (J) = Integration of flow (L), Pressure (kPa) and Time (sec).
3.1.6 Summary of Parameters From 6-minute Trial

The regulation of respiration had been described earlier (Section 1.2), the following parameters are calculated during the initial use of the 6-minute trial protocol to assess increases in ventilation and work required by the respiratory system as a result of the intensity of a trial. In a steady state trial these parameters would be expected to adapt to the level and pattern of ventilation required and remain constant throughout. The level of adaptation should allow the intensity of the trial to be assessed in different individuals; such as in health and disease, and in different modes; such as when seated or exercising. Initial increases in ventilation are achieved by increases in both VT₁ and fᵣ and represent the respiratory systems main way of adapting to increased demand.

1) VT₁ (L).

VT₁ is dependent on the size of the lungs and height. In all subjects however there is a physical limit to which VT₁ can increase to meet ventilatory demands. Although the respiratory system is generally described as being ‘over engineered’ and levels of VT₁ rarely meet the levels seen during maximal ventilation, even during maximal exercise tests.

2) Increases in respiratory rate allow the respiratory system to adapt to increased ventilatory requirements when VT₁ can either be no longer increase or the increased demands for ventilation can be met by an increase in fᵣ (min⁻¹) for example that during exercise. Normal resting fᵣ for example that seen in Section 5.4.3 is on average 16±4 bpm⁻¹, although this is elevated in disease such as COPD 20±4 bpm⁻¹ (Colsanti et al 2004) and during maximal exercise can reach 51 bpm⁻¹ (Kift & Williams 2007).

3) Wᵣ/t₁ (J.sec⁻¹) represents the energy used by the respiratory system when standardised for the period of inspiration time. If energy increases but VT₁ and fᵣ remain the same the respiratory system increases driving pressure of the system. As it is dependent on the volume of ventilation it is necessary to express the energy needed to move a volume of air as work.

4) VT₁/t₁ (L.sec⁻¹) represents an index of the demand on the respiratory system (Millic-Emili & Grunstein 1976)
5) Measuring the work of breathing described earlier (Section 1.12) is complex as quantifying movement and distortions of the chest wall are difficult to quantify and as such work of breathing measured at the mouth is not a direct measure of the work of breathing. However ‘measuring the work performed against an external load can provide sufficient information for purposes of respiratory endurance testing’ (ATS, 2002). \( \text{InWrs}^{\text{mouth}} \) (J.L) can therefore be used as a measure of endurance of respiratory system.

3.2 Resting Tidal Breathing Profile Analysis

Resting tidal airflow was recorded in seated subjects breathing through a mouthpiece and wearing a nose-clip for 3-minutes (Section 2.3.9). The mouthpiece was connected in series with a low-resistance screen pneumotachograph. The principle of the pneumotachograph rests on Poiseuille's Law, which states that, under capillary conditions, in a straight rigid tube, delivery is proportional to pressure loss per unit of length. The continuous measurement of the pressure loss, that is the measurement of the pressure difference between two points on the tube, is a function of gas of the rate of gas flow (ARTP 2006). When airflow is integrated with time, volume can be calculated.

A differential pressure sensor (PowerLab, ADInstruments) allowed respiratory flow to be logged at 100 Hz onto a computer and saved for later analysis (Fig 3.12). After recording resting tidal airflow, the data logging software (Chart V5, ADInstruments) was used to extract the final minute of the continuous flow signal for export as text files. This was to allow participants to achieve a rested breathing pattern.

Proprietary software was used to further process the flow data into individual breaths and exclude unusually large or small breaths. This software was used to overcome the important issue when assessing resting tidal profile of the correct selection of the tidal flow loops or curves to assess (see Section 2.3.7). The breaths were summed to form a single representative breath from which a series of time and flow metrics were derived (Fig 3.13). Parameters are as follows: duration of inspiration, \( t_I \) (a-c); duration of expiration, \( t_E \) (c-e); duration of breath, \( t_{Tot} \) (a-e); time to reach peak flow during inspiration, \( t_{PTIF} \) (a-b) and expiration, \( t_{PTEF} \) (c-d); peak flow rate at inspiration, PIF (f) and expiration, PEF (g). A further flow profile indice, \( t_{PPEF80} \), was derived from the expiratory phase of this representative breath. This time point at 80% of peak
expiratory flow rate (I in Fig 3.13) was used to define changes in flow rate as a decrease in $t_{PPEF80}$ suggests airflow obstruction and hyperinflation (Colsanti et al. 2004).

### 3.2.1 TBPA Outcomes

Using regression analysis Colsanti et al (2004) developed predictive formulas using parameters measured from resting tidal breathing profile to calculate FEV$_1$ expressed as FEV$_1$ from Tidal Airflow Profile – FEV$_{1TAP}$ (Table 3.1).

#### Table 3.1: Equations Used to Calculate FEV$_{1TAP}$ in Healthy Controls and COPD.

*A = age (years); H = height (metres)*

<table>
<thead>
<tr>
<th>Regression Equation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>FEV$<em>{1TAP} = -5.41 + (H \times 4.97) + (A \times -0.02) + (t</em>{PTEF} \times 0.005)$</td>
</tr>
<tr>
<td>COPD</td>
<td>FEV$<em>{1TAP} = -3.73 + (t</em>{PPEF80} \times 0.031) + (t_{PIF} \times 6.08) + (Age \times -0.017)$</td>
</tr>
</tbody>
</table>
Figure 3.12: Example of Continuous Resting Tidal Air flow

Figure 3.13: An Example of a Normal Resting Adult Tidal Flow Profile.
3.3 Metronomic Control of Breathing

Initially an open source standard electronic metronome (available on-line http://www.bestsoftware4download.com/software/t-free-metronome-download-gmobovun.html) was used to set the required $f_R$, by providing a visual cue and audible tone (Fig 3.14). The subjects were instructed to inspire and expire on each subsequent tone. As standard metronomes generate a constant (symmetrical) tempo, this meant that subjects should maintain a constant $t_I/t_{Tot}$ of 0.5.

Existing studies (Section 2.2.12), when attempting to control the breathing pattern often failed to explicitly state a $t_I/t_{Tot}$ ratio. The most commonly stated ratio was 0.5, i.e. when the phase of expiration equals that of inspiration, however in healthy individuals average $t_I/t_{Tot}$ is closer to 0.4 (Williams et al 2000) where inspiration is approximately 40% of total breath time.

An extensive search for further available metronomes was undertaken and many physical and electronic versions were identified. It was unusual however to find a metronome that was designed to operate at the slow tempo of a resting breathing rate 8 – 20 beats per minute as most were designed for musicians who require substantially higher beat tempos. Only one specialised commercially available respiratory metronome could be located (RESPERATE - www.resperate.co.uk), but this is a complex device used to lower blood pressure (Schein et al 2001) and therefore is not suitable for use in this context.

Subsequently a bespoke metronome was developed, that would specifically allow the proportion of time during the two phases of respiration to be set independently from the overall tempo of breathing. For example this device would allow participants breathing to be paced, both $f_R$, and inspiratory and expiratory phase, by providing a computer generated visual cue and audible tone to signify the start of each inspiration and expiration. Separation of inspiration or expiration allowed the desired $t_I/t_{Tot}$ ratio to be set at the operator’s choice. Written in Microsoft Visual Basic, this Variable Electronic Metronome (VEM) was developed over three versions, the final version incorporated a colour indicated change red/green, with $f_R$ and $t_I/t_{Tot}$ fully selectable (Fig 3.15).
3.4 Standard Lung Function Measurements

Standard techniques that are used to assess respiratory function are outlined in Section 1.5. Forced Expiratory Volumes (Fig 3.16) were measured using a range of spirometers; all were routinely calibrated before use and standardised to BTPS.

3.4.1 Measures of Dynamic Lung Function

All subjects performed maximal expiratory manoeuvres as per British Thoracic Society standards (1994); specifically while seated and wearing a nose clip, all subjects were instructed to inhale to Total Lung Capacity (TLC) then insert mouth piece and expire as forcefully as possible to residual volume. Three measurements were made with the highest being used for subsequent analysis, with FEV\textsubscript{1} and FVC being recorded.
3.4.2 Spirometry Reference Values

Results obtained from spirometry are of relatively limited use unless there is a value for a ‘normal’ subject of similar sex, age and height that can be used for comparison. Large population studies have been undertaken to obtain reference values which enable mean or average values to be calculated (ARTP 2006) those developed by the European Community for Steel and Coal – ECSC (Quanjer et al 1993) were used in this thesis when studying adult subjects >18 years (Table 3.2). When assessing children’s lung function (Chapter 8) equations developed by Rosenthal et al (1993) were used to predict relevant reference values.

Table 3.2: ECSC Spirometry Reference equations for FEV$_1$ and FVC (L)

\[ h = \text{height (cm)}; \ a = \text{age (years)} \]

<table>
<thead>
<tr>
<th></th>
<th>Regression Equation</th>
<th>(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>[(0.0576 \times H) - (0.026 \times A) - 4.34]</td>
<td>(± 0.61)</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>[(0.043 \times H) - (0.029 \times A) - 2.49]</td>
<td>(± 0.51)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>[(0.0443 \times H) - (0.026 \times A) - 2.89]</td>
<td>(± 0.43)</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>[(0.0395 \times H) - (0.025 \times A) - 2.60]</td>
<td>(± 0.38)</td>
</tr>
</tbody>
</table>

3.4.3 Measures of Static lung function and Airway Resistance

Participants were asked to sit in a sealed and calibrated Body Box (Master Screen Body, Jaeger, Germany) for 1 minute to allow temperature to equilibrate before testing. Whole body plethysmography was then used to measure participants Total Lung Capacity, Residual Volume, Functional Residual Capacity. Definitions and illustrations are described below (Fig 3.17). Whole body plethysmography was also used to assess participants air flow resistance $R_{AW}$ (Goldman et al 2005).
Figure 3.16: **Forced Expiratory Tests:** Forced Expiratory Volume in one second (FEV₁). The volume of gas expired during the first second of a forced expiration following a full inspiration. Forced Vital Capacity (FVC). The volume of gas expired when the forced expiratory manoeuvre is continued to full expiration.

Figure 3.17: **Static Lung Function Tests (adapted from McConnell 2007)**
Total Lung Capacity (TLC). Volume of air in the lungs at full inspiration; Residual Volume (RV). The volume of air remaining in the lungs at the end of a full expiration; Functional Residual Capacity (FRC). The Volume of air remaining in the lungs after
resting tidal breath; Expiratory and Inspiratory Reserve Volumes (ERV/IRV) The volumes of air available between the beginning or end of a tidal breath and TLC and RV respectively; Tidal Volume ($V_T$). Volume of air in a single breath.

### 3.5 Standard Exercise Tests

A variety of methods are available for assessing the respiratory and cardiovascular response to exercise. These are useful as they represent a standardised stressor which results in an increased requirement on the respiratory system that is represented by an increase in the ventilation rate as the body’s demand for oxygen increases. Using established tests not only gives this standardised stressor but can, with maximal tests (measure) or with sub-maximal tests (predict) maximal oxygen uptake ($\dot{V}O_2\text{ max}$) which can then be used as a measure of aerobic fitness.

#### 3.5.1 Maximal Oxygen Uptake ($\dot{V}O_2\text{ max}$) Testing

Maximum oxygen uptake is the highest value of oxygen that can be attained and measured during an incremental exercise test. It requires an extensive laboratory environment with calibrated ergometers (cycle or treadmill), exhaled gas analysis devices, equipment suitable to measure large $V_E$’s (as opposed to the smaller $V_E$’s seen at rest) and trained staff to administer test protocols.

As attainment of $\dot{V}O_2\text{ max}$ generally necessitates the use of large muscle groups over an extended period of time 5–15 min, when the body is working aerobically, hence $\dot{V}O_2\text{ max}$ is also described as maximum aerobic capacity (Cooper & Storer 2005). It is a widely used measure and considered the ‘gold standard’ method of assessing human exercise performance (James et al. 2007)

#### 3.5.2 Astrand - Rhyming Test (Astrand & Rhyming 1954)

The Astrand - Rhyming test is a single 6-minute stage cycle protocol developed to elicit a steady state exercise response by cycling at a set pedal cadence against a resistance to achieve a predetermined work rate. The test requires a cycle ergometer and means of assessing participants heart rate ($f_H$). Using the linear relationship between heart rate and oxygen consumption $\dot{V}O_2\text{ max}$ can be predicted.
3.5.3 6-minute Walk Test (ATS 2002B)

The 6MWT is a practical simple test that requires a corridor with a known distance, ideally 30 metres but can be 10 – 25 metres. No other exercise equipment or advanced training is necessary making it useful for clinical use within hospitals. As walking is an activity performed daily by all but the most severely impaired patients it is a modality that most patients can undertake.

This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6-minutes. It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing.

The self-paced 6MWT assesses the sub-maximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at sub maximal levels of exertion, the 6MWT may better reflect the functional exercise level for daily physical activities.
### Summary & Conclusion

#### In Summary……..
In this chapter I have outlined the testing methodologies that will be used in the rest of the thesis.

#### The Participant
- A 6-minute trial is similar to other existing physiological tests in terms of time and intensity and should therefore be able to completed by the majority of participants.

#### The Test
- TBPA has been developed as technique to predict $FEV_1$ from relaxed tidal breathing.
- The $R_K$ device is able to measure $f_R$, $W_I$ & $InW_{rs}^{mouth}$.
- Work of breathing at the mouth ($InW_{rs}^{mouth}$) can be used as an indirect measure of respiratory endurance.

The methods that will be used in this thesis are outlined. The two main protocols, the 6-minute $R_K$ trial and TBPA, and the two outcome parameters $InW_{rs}^{mouth}$ and $FEV_{1TAP}$ are described. Existing methods of lung function are also described which can be used to differentiate between health and disease. These are useful for comparison and to differentiate between individuals, but in themselves do not represent measures of endurance. $FEV_1$ however provides a direct comparison for TBPA analysis.
Chapter 4 - Control Subjects

4.0 Introduction and Overview

This chapter describes the development and refinement of the 6-minute trial outlined earlier (Section 3.1.3.2). Initially the steady state nature of the protocol is examined and outcome parameters tested. Following this the level of R_K needed to elicit a suitable response is elucidated and the effect that this level of R_K has on lung hyperinflation is measured. The effect of standardising f_R, t_I/t_Tot and phase loading is then assessed so that a standard protocol can be created. This protocol is then examined in control subjects.

4.1 Development and Analysis of a 6-minute Breathing Protocol

4.1.1 Introduction

Respiratory system endurance can only be accurately measured whilst undergoing a steady rate of respiratory work. Current incremental and maximal test protocols do not achieve this steady-state and therefore can only provide a measure of the respiratory system’s strength and susceptibility to fatigue, and thus not a measure of endurance (Section 1.9). Published examples of whole body sub-maximal exercise tests that elicit a steady work rate were used to inform the initial time frame for the 6-minute protocol (Section 3.1.3).

Studies that assess the time to reach peak expiratory flow, t_PTEF generally have used much shorter sample times, although this was most likely due to the neonates and children studied (see Section 2.3.7). In comparable studies of adults, sample rates ranged from 80 seconds (Morris et al. 2004) to 2 minutes (Williams et al 2000). These
protocols were short as only resting tidal flow patterns were measured, and it was assumed that a steady-state would be already present.

The aim of the following study was to assess whether participants achieved a steady state, assessed by measuring the breath-to-breath change in the parameters described in Section 3.1.6; $V_{T1}$, $W_{I}/I$, $V_{T1}/t_{I}$ and $InWrs_{mouth}$ throughout a 6-minute trial.

There were two primary questions; 1) how long does it take for test participants to enter into a steady respiratory rate, and 2) which segment of the 6-minute trial best represents the participant’s response to the trial?

**4.1.2 Method**

*Participants*
Forty healthy individuals (9F:31M; age range 18-64 yrs; FEV$_1$ % pred 103 ± 13; MIP 105 ± 34 cm H$_2$O) undertook a 6-minute seated trial (Section 3.1.3.2). Upon gaining consent, body weight and height were measured and baseline spirometry performed (Section 3.4.1).

*Protocol*
A standard protocol was followed (Section 3.1.3.2) and the $R_k$ load was set at 0.75 kPa.L.sec$^{-1}$.

*Data Analysis*
At the end of the test the following study parameters were per breath calculated; $V_{T1}$ (ml) $W_{I}/I$ (J.sec$^{-1}$), $V_{T1}/t_{I}$ (L.sec$^{-1}$) and $InWrs_{mouth}$ (J.L) (Section 3.1.6). The values for each parameter for the last ten breaths of each trial were averaged and used to normalise the data, allowing a comparison of the absolute change in each breath from this average value to be calculated. The number of breaths when each study parameter was outside ± 2 SD of the average of the normalised values were summed.

**4.1.3 Results**
Participants tolerated the 6-minute protocol well and successfully completed all forty trials with none being stopped early and no adverse effects reported. The average respiratory rate per for the forty trials was 10 ± 5 breaths per minute.
The total numbers of breaths outside ± 2 SD for VT\textsubscript{1}, WI/\textit{t}\textsubscript{1}, VT/\textit{t}\textsubscript{1} and InWrs\textsuperscript{mouth} were 2, 4, 2 and 5 respectively, of which around half occurred within the first ten breaths for each parameter (Figure 4.1).

**Figure 4.1: Change in (A) VT\textsubscript{1} (ml), (B) WI/\textit{t}\textsubscript{1} (J.sec\textsuperscript{-1}), (C) VT/\textit{t}\textsubscript{1} (L.sec\textsuperscript{-1}) and (D) InWrs\textsuperscript{mouth} (J.L), for each breath over 6 minutes.** Upper solid line represents + 2 SD, Lower solid line represents – 2 SD, grey dashed line represent zero.

### 4.1.4 Conclusions

This data shows that during a 6-minute protocol using a constant R\textsubscript{K} load of 0.75 kPa.L.sec\textsuperscript{-1}, participants enter into a steady state of respiration as seen by a constant VT\textsubscript{1}, WI/\textit{t}\textsubscript{1}, VT/\textit{t}\textsubscript{1} and InWrs\textsuperscript{mouth}. The majority of any deviation was seen to occur within the initial ten breaths, and for participants who completed these trials this would equate to approximately the first minute of the trial (average f\textsubscript{R} = 10 ± 5 min\textsuperscript{-1}).

This initial deviation most likely represents the period of adaptation to the increased resistive load. To ensure that the sampled data is representative of a steady state of
respiration it is necessary when using a 6-minute protocol to disregard the initial ten breaths from the analysis and use the remaining breaths to calculate study parameters. To ensure this represented a common factor, the first minute of data should not be used in the analysis of any RK trials.

While all participants successfully completed the 6-minute protocol, there were anecdotal reports of increased salivation and some mild discomfort whilst breathing through the RK device. This is likely to occur as when breathing solely through the mouth, participants would be unable to moisten the air by breathing nasally and swallowing excess saliva is difficult.

The aim was to develop a protocol that would be easy and comfortable to undertake, while ensuring the participants had entered into steady state. Previous studies of respiratory endurance identified in the literature review have suggested protocols of 10-minutes or more are necessary, however this data shows that a 6-minute protocol is a suitable time period to elicit a steady state response.
4.2 Applying Incremental $R_K$ During 6-minute Trial

4.2.1 Introduction

To accurately quantify endurance by eliciting a steady work rate, the optimal level of resistance needs to be applied. This would be a resistance that is sufficient to provoke a quantifiable change in the respiratory parameters that can be constantly maintained during the 6-minute trial (Section 3.1.3.2). There is a need to optimise the $R_K$ load, as too small a load would not alter the respiratory parameters while too high a load would result in an incremental pattern of work possibly resulting in fatigue and preventing the attainment of a steady work rate.

In Section 4.1 an $R_K$ of 0.75 kPa.L.sec$^{-1}$ was shown to elicit a steady state response, but is this the optimum $R_K$ load? Repeated 6-minute trials with a range of $R_K$ loads were made to assess the minimum $R_K$ load that elicited a significant increase in study parameters compared with trials were no resistance was added, i.e. with an $R_K$ load of 0, just the resistance provided by the fully open orifice and the intrinsic airway resistance of a participant.

4.2.2 Method

Participants

Thirty two healthy individuals (4F:28M; age range 18-64 yrs; FEV$_1$% pred 104±14) undertook a series of 6-minute seated breathing trials (Section 3.1.3.2). Upon gaining consent, body weight and height were measured and baseline spirometry performed (Section 3.4.1).

Protocol

The standard 6-minute protocol was followed (Section 3.1.3.2). The first five subjects undertook six separate 6-minute trials at $R_K$ of; 0, 0.25, 0.5, 0.75, 1 and 1.5 kPa.L.sec$^{-1}$ administered in a varied sequence to negate any order effect. On the outcome of these trials the remaining subjects (n=27) undertook trials at $R_K$’s of 0, 0.75 and 1.5 kPa.L.sec$^{-1}$ again in a varied sequence. Study parameters were calculated for each breath from the continuous data (Section 3.1.6.) with the first minute of data being discarded from the analysis (Section 4.1.4).
Data Analysis

A one way ANOVA was used to assess for differences at increased $R_K$ from 0 kPa.L.sec$^{-1}$. When significance was identified a Holms-Sidak Post-hoc test was applied.

4.2.3 Results

Participants tolerated the 6-minute trials at varying $R_K$ well and successfully completed all trials with none being stopped early and no adverse effects reported. Data was lost for one trial due to a technical malfunction of the $R_K$ device.

4.2.3.1 Initial 30 Trials (participants n=5)

There was no difference between trials in terms of $f_R$, $V_{T_{1}}$, and $V_{T_{1}}/t_{1}$, while $\ln W_{rs}^{mouth}$ and $W_{r}/t_{1}$ were seen to significantly increase in trials with $R_K$ loads above 0.75 and 1.0 kPa.L.sec$^{-1}$ respectively (Fig 4.2). With rest phases in between the 6 trials, cumulative testing time was in excess of 60-minutes. This data shows that only loads above 0.75 kPa.L.sec$^{-1}$ were able to initiate differences in response therefore the remaining subjects completed three trials at $R_K$ loads of 0, 0.75 and 1.5 kPa.L.sec$^{-1}$.

4.2.3.2 All 89 trials (participants n = 32)

With a greater number of participants and trials completed the findings from the initial trials was confirmed, with significant differences observed only in $\ln W_{rs}^{mouth}$ and $W_{r}/t_{1}$ with trials with $R_K$ loads of 0.75 kPa.L.sec$^{-1}$ and above (Fig 4.3).
Figure 4.2: The mean ± SD is shown for A) \( f_R \) (min\(^{-1}\)), B) \( VT_1/t_1 \) (L.sec\(^{-1}\)), C) \( W/t_1 \) (J.sec\(^{-1}\)), D) \( VT_1 \) (L) and E) InWrs\(^{mouth}\) (J.L) during 6-minute trials (n=30) at six increasing \( R_k \) loads (kPa.L.sec\(^{-1}\)). *significantly different (p<0.05) from trial with \( R_k \) load of 0 kPa.L.sec\(^{-1}\).

Figure 4.3: The mean ± SD is shown for A) \( f_R \) (min\(^{-1}\)), B) \( VT_1/t_1 \) (L.sec\(^{-1}\)), C) \( W/t_1 \) (J.sec\(^{-1}\)), D) \( VT_1 \) (L) and E) InWrs\(^{mouth}\) (J.L) during 6-minute trials (n=89) at three increasing \( R_k \) loads (kPa.L.sec\(^{-1}\)). * significantly different (p<0.05) from trial with \( R_k \) load of 0 kPa.L.sec\(^{-1}\).
4.2.4 Discussion

The application of an $R_k$ load of 0.75 kPa.L.sec$^{-1}$ significantly increased $\text{lnWrs}_{\text{mouth}}$ and $W_i/t_i$ from that seen when no resistance was applied ($R_k = 0$ kPa.L.sec$^{-1}$), increasing from -0.15 to -0.33 (J.L) and 0.06 to 0.12 (J.sec$^{-1}$) respectively. These results suggest that this is the lowest $R_k$ load that can be applied to elicit a significant physiological response in the work of breathing as assessed by $\text{lnWrs}_{\text{mouth}}$ and $W_i/t_i$.

The initial 6 trials represented a cumulative testing time of over 60-minutes. This prolonged time could possibly provoke some form of testing fatigue although the maximum number and length of breathing trials that can be used remains unclear with some authors suggesting no more than three short trials (Wiley & Zechman 1966). However by varying the order in which the loads were administered confidence can be maintained that these differences were due to $R_k$ load and the response would be similar in all subjects.

For the second part of this study the number of trials was reduced to make widespread testing more feasible and logistically possible. Increasing the number of participants from 5 to 32 confirms the initial results that an $R_k$ load of 0.75 kPa.L.sec$^{-1}$ represents a suitable load to use in a 6-minute trial. However whether this is the ‘best’ load is still unclear as this could be somewhere between 0.5 and 0.75 kPa.L.sec$^{-1}$. Further trials could be undertaken to further identify such a point, varying $R_k$ load by 0.5 or 0.10 kPa.L.sec$^{-1}$ rather than 0.25 kPa.L.sec$^{-1}$ used in this study. It remains that all participants successfully completed all trials at 0.75 kPa.L.sec$^{-1}$ and that this was seen to elicit a significant increased work of breathing in all participants.

In these healthy participants the inspiratory work of breathing increased with increasing $R_k$, with the $\text{lnWrs}_{\text{mouth}}$ increasing 4 fold between 0 to 1.5 kPa.L.sec$^{-1}$. As no concomitant increase in $f_R$ or $V_TI$ was shown, the extra work of breathing must have been met by an increased driving pressure generated by the respiratory muscles.
4.3 Pulmonary Hyperinflation in Healthy Adults Breathing Against a \(R_K\) Load

4.3.1 Introduction

It has been shown that significant increases in \(\text{InWrs}^{\text{mouth}}\) and \(W/L_t\) are provoked by applying an \(R_K\) of 0.75 kPa.L.sec\(^{-1}\) or more (Section 4.2). This \(R_K\) load has to be higher than the inherent airways resistance (\(R_{AW}\)) found in the healthy lung which is approximately 0.2 kPa.L.sec\(^{-1}\) (Cloutier 2007). In obstructive airway disease, such as COPD, the intrinsic \(R_{AW}\) is higher than this normal value. This requires greater pressure generation to overcome this resistance and a common strategy adopted by people with COPD is to develop a progressive static hyperinflation of the lungs. The raising of FRC helps to reduce the increased work of breathing (Cooper 2008).

This study aims to address the question; Do healthy subjects respond in a similar way to increased \(R_{AW}\)? (applied via the application of increased \(R_K\)). The effect on lung volumes whilst breathing through the \(R_K\) device was assessed.

4.3.2 Methods

Participants & Protocol

Eleven healthy individuals (5F:6M: FEV\(_1\) % pred 105 ± 13) underwent spirometry (Section 3.4.1) and whole-body plethysmography (Master Screen Body, Jaeger, Germany) allowing the Functional Residual Capacity (FRC), Residual Volume (RV) and Total Lung Capacity (TLC) and \(R_{AW}\) to be assessed (Section 3.4.2).

The \(R_K\) device was then attached distally to the occlusion valve (Figure 4.4), FRC measurements were then repeated while the \(R_K\) device applied increasing loads as described previously 0, 0.25, 0.5, 0.75, 1 and 1.5 kPa.L.sec\(^{-1}\) (Section 4.2.1).

Data Analysis

A one way ANOVA was used to assess for significant (p<0.05) differences in FRC, TLC, RV and \(R_{AW}\) when an \(R_K\) load was applied and when there was no added resistance (NAR). When significance was identified a Holms-Sidak Post-hoc test was applied.
4.3.3 Results

The 11 participants tolerated the manoeuvres well and all seventy-seven tests were successfully completed. With exposure to increasing R_K during the seven different resistive loads, the participants’ TLC and RV did not change, while the FRC increased significantly with an R_K above 0.5 kPa·L·sec\(^{-1}\) (p<0.05) (Fig 4.5).

As expected, when the R_K device was attached the participants’ R_{AW} was seen to significantly increase when compared to the initial trial with no added resistance, NAR (Fig 4.6). When the NAR trial was discarded R_{AW} was seen to increase in trials when the R_K load was above 0.75 kPa·L·sec\(^{-1}\).

The average R_AW = 0.32 ± 0.19 kPa·L·sec\(^{-1}\) was slightly higher than the ‘normal average’ from Cloutier (2007) but was similar to the value given by Jaeger (Manufacturer of the body plethysmography box used), which give all healthy subjects a predicted R_{AW} of 0.3 kPa·L·sec\(^{-1}\).
4.3.4 Discussion

The significant increases observed in FRC illustrates how the lungs hyper-inflate as \( R_K \) increases. Interestingly the significant difference in FRC begins at a lower level of \( R_K \) (0.5 kPa.L.sec\(^{-1}\)) than the \( R_K \) level (0.75 kPa.L.sec\(^{-1}\)) at which significant increases were observed in \( \text{InWrs}^{\text{mouth}} \) (Section 4.2.3). This suggests that the change in lung mechanics resulting from the initial increases in FRC absorbs the higher work demand imparted by the raised \( R_K \). Then as the \( R_K \) increases the raised FRC no longer helps and \( \text{InWrs}^{\text{mouth}} \) has to increase instead. This data combined shows the healthy respiratory system responds to applied \( R_K \) loads through an increased work of breathing and hyperinflation, a response similar to that found in patients with obstructive disease (O’Donnell & Laveneziana. 2006).

**Figure 4.5:** TLC (■), FRC (●) and RV (▲) During Trials With No Added Resistance (NAR) and Increasing \( R_K \). The mean ± SD is shown for 11 participants. *Significantly different (p<0.05) from trial with NAR.*
Figure 4.6: Panel A) Airway Resistance, $R_{AW}$ (kPa.L.sec$^{-1}$) & Panel B) $R_{TOT}$ (kPa.L.sec$^{-1}$) During Trials With No Added Resistance (NAR) and Increasing $R_K$.

Mean ± SD shown for 11 participants. *Significantly different (p<0.05) from trial with NAR; ^ significantly different (p<0.05) for loaded trials when compared to 0 $R_K$. 
4.4 Effect of Varying Respiratory Rate

4.4.1 Introduction

There is no one standardised technique for assessing non-invasive respiratory endurance (Section 2.2.8) and this has resulted in a range of non-invasive test modalities and measures (Hart 2005), plus a variety of intensities being used. So far in this thesis it has been shown that an \( R_k \) load of 0.75 kPa.L.sec\(^{-1} \) is sufficient to elicit a significant response in \( \text{In}W_{rs}^{\text{mouth}} \) and \( W_{I/tI} \) during a 6-minute trial (Section 4.2) in which the participants breathing was unpaced. It is still unclear if the participants breathing rate should be controlled or standardised while undertaking a trial.

There exists diversity in the breathing pattern of awake humans at rest, alongside breath-to-breath fluctuations in ventilatory variables (Benchetrit 2000). Therefore the following questions should be asked; 1) How should a steady-state test of respiratory system endurance be standardised; and 2) What ventilatory variables need to be or should be controlled?

There is little consensus on what is the optimal respiratory rate (\( f_R \)) (Section 2.2.12). Paced breathing when measuring prolonged tests of loaded respiratory function has been highlighted as a means of helping to control test variability (Rohrbach et al. 2003). Furthermore Rochester (1988) states that when testing respiratory muscle endurance ‘no matter what kind of load is imposed, the breathing pattern must be rigidly controlled’. This study aimed to assess the impact of an imposed breathing rate, \( f_R \) on the integrity of the 6-minute test protocol.

4.4.2 Method

Participants

Ten healthy individuals (4F:6M; age range 25-64 yrs; FEV\(_1\) % pred 105 ± 14) undertook a series of 6-minute seated trials using described methods (Section 3.1.3.2). Upon gaining consent, body weight and height and spirometry were measured (Section 3.4.1).

Protocol

Participants made two study visits at least one week apart. On their first visit they undertook three 6-minute trials at \( R_k \) loads of 0, 0.75 and 1.5 kPa.L.sec\(^{-1} \) in a varied sequence (to negate order effect) with their \( f_R \) either paced or unpaced. They
completed the alternate trials (-paced or unpaced) in the same order on the following visit. Study parameters were calculated per breath from data (Section 3.1.6.) with the first minute of data being discarded from the analysis (Section 4.1.4).

Paced Breathing Protocol

For paced breathing trials, an open source standard electronic metronome (SEM) was used to set the required $f_R$, by providing a visual cue and audible tone (Section 3.3). The participants faced a screen displaying the SEM and were instructed to breathe in and out on each subsequent tone. This paced $f_R$ at 15 bpm and $t_I/t_{Tot}$ at 0.5.

Unpaced breathing protocol

Participants were given no instruction during any of these trials on their expected $f_R$ or $t_I/t_{Tot}$ ratio and therefore maintained a self-paced or volitional rate throughout.

Data Analysis

A two way ANOVA was used to assess for statistical difference between $R_K$ loads during paced versus unpaced breathing. When significance was identified a Holm-Sidak Post-hoc test was applied.

4.4.3 Results

Participants tolerated the protocol well and successfully completed all sixty trials with none being stopped early and no adverse effects reported. During unpaced trials $f_R$ and $t_I/t_{Tot}$ were significantly lower ($p < 0.05$) than the target rate for the SEM paced trials (Table 4.1). There was no difference between paced and unpaced trials in any other parameter at any of the three applied $R_K$ loads.

During both paced and unpaced trials only $W/t_I$ (Table 4.4) and $InWrs_{mouth}$ (Figure 4.7) were seen to significantly increase as the $R_K$ load increased. $f_R$, $t_I/t_{Tot}$, $V_{T1}$ and $V_{T1}/t_I$ remained constant irrespective of the $R_K$ load.
Table 4.1: Parameters at End of 6-minute Trials at Increased $R_K$, expressed as mean± SD† significantly different from self paced trials *significant difference from trial at $R_K$ 0 kPa.L.sec$^{-1}$. (P<0.05).

<table>
<thead>
<tr>
<th>$R_K$ (kPa.L.sec$^{-1}$)</th>
<th>0</th>
<th>0.75</th>
<th>1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-paced Breathing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$f_R$ (min$^{-1}$)</td>
<td>14±5</td>
<td>11±3</td>
<td>11±4</td>
</tr>
<tr>
<td>$t_I/t_{Tot}$</td>
<td>0.39±0.05</td>
<td>0.42±0.03</td>
<td>0.42±0.04</td>
</tr>
<tr>
<td>$VT_I$ (ml)</td>
<td>730±203</td>
<td>693±217</td>
<td>748±252</td>
</tr>
<tr>
<td>$VT_I/t_I$ (L.sec$^{-1}$)</td>
<td>-0.35±0.07</td>
<td>-0.28±0.07</td>
<td>-0.29±0.06</td>
</tr>
<tr>
<td>$W_I/t_I$ (J.sec$^{-1}$)</td>
<td>0.04±0.02</td>
<td>0.09±0.03†</td>
<td>0.19±0.08*</td>
</tr>
</tbody>
</table>

| **Paced Breathing at 15 bpm$^{-1}$** |     |      |     |
| $f_R$ (min$^{-1}$)       | 15±0.4† | 14±1.0† | 15±0.4† |
| $t_I/t_{Tot}$             | 0.45±0.05† | 0.45±0.03† | 0.46±0.04† |
| $VT_I$ (ml)               | 653±190 | 623±206 | 623±177 |
| $VT_I/t_I$ (L.sec$^{-1}$) | -0.37±0.07 | -0.33±0.10 | -0.33±0.10 |
| $W_I/t_I$ (J.sec$^{-1}$)  | 0.07±0.05 | 0.12±0.07* | 0.23±0.11* |

Figure 4.7: InWrs$^{mouth}$ (J.L) During Paced (black bars) and Unpaced (grey bars) Breathing at Increased Resistances. * significantly different (P<0.05) with $R_K$ trials at 0 kPa.L.sec$^{-1}$.
4.4.4 Discussion

During 6-minute trials an R_K load of 0.75 kPa·L·sec^{-1} was used to increase W/I and InWrs_{mouth}, VT_{I} was seen to remain constant as has been observed previously (Section 4.2). During paced trials a metronome was able to keep participants f_R at 15 bpm^{-1}, although f_R significantly decreased in trials without the metronome when breathing was unpaced. Although the metronome also paced t_I/t_{Tot}, average t_I/t_{Tot} values were below 0.5 indicating that while the metronome successfully paced f_R it was more difficult to accurately control the ratio t_I/t_{Tot}. However it was found that W/I and InWrs_{mouth} were constant irrespective if f_R was paced or unpaced. InWrs_{mouth} was seen to significantly increased as R_K load increased above an average healthy participants own inherent airway resistance (average healthy participants R_{eff} = 0.32 ± 0.19 kPa·L·sec^{-1}, Section 4.3.2).

These data suggest that when assessing respiratory system endurance the participant should breathe at their own volitional rate as there is no difference in any outcome apart from a decreased f_R. This would suggest that a more efficient breathing style is allowed when participants are unpaced i.e. they use less breaths to do the same amount of work.

When using an applied R_K to assess InWrs_{mouth} allowing participants to set their own f_R will not only result in more efficient breathing it would make this method simple to apply, requiring less equipment and reducing the amount of instruction needed for participants. This would be important within a clinical setting, as it would remove a large part of the volitional element of the test, with only a time limit being imposed allowing a more “brain” centred response by the participant (Noakes 2008). This should make the application of this test in patients with obstructive lung diseases such as COPD easier, allowing them to match their own volitional breathing rate. While healthy participants breathe at 15 min^{-1}, patients with airway obstruction tend to breathe faster at around 20 min^{-1} (Colsanti et al. 2004).
4.5 Effect of $R_K$ Load During Separate Phases of Tidal Breathing

4.5.1 Introduction

There is little consensus on what is the optimal duty cycle $t_I/t_{Tot}$ that should be used during any respiratory endurance test (Section 2.2.12). Paced breathing when measuring prolonged tests of loaded respiratory function has been highlighted as a means of helping to control test variability (Rohrbach et al. 2003) although it has been shown that trial outcomes remain constant irrespective of $f_R$ being paced or unpaced.

Previous studies have attempted to control $t_I/t_{Tot}$ even though standard metronomes are symmetrical i.e. if breathing is initiated on subsequent indications (clicks or ticks etc) it would pace the two phases of breathing equally. This would result in a $t_I/t_{Tot}$ ratio of 0.5, which is unnatural at rest. Furthermore many metronomes are not designed to operate at the lower pacing levels that are applicable to those of breathing at rest, approximately 8-30 breaths per minute, but are specifically designed for musicians’ at considerably higher tempos. This drove the development of a variable electronic metronome (VEM) described earlier (Section 3.3).

This study aimed to establish in healthy individuals the effect varying of $t_I/t_{Tot}$ on ventilation and the work of breathing during the 6-minute test of endurance previously outlined (Section 4.4). Additionally the utility and reliability of this variable electronic metronome to control individual’s $t_I/t_{Tot}$ was assessed.

4.5.2 Method

Participants

Fifteen healthy participants (8F;7M; age range 20-31yrs; FEV$_1$ % pred 106 ± 8) undertook 6-minute seated trials (Section 3.1.3). Upon gaining consent, body weight and height were measured and baseline spirometry performed (Section 3.4.1).

Protocol

Initially participants were asked to breathe, whilst seated, through a pneumotachograph for 3 minutes (ADInstruments, UK) allowing the self-paced $f_R$ and $t_I/t_{Tot}$ to be calculated. For the variable phase loaded trials a bespoke variable electronic metronome (VEM) was used (Section 3.3). This metronome was designed to pace both $f_R$ and breathing pattern by providing a computer generated visual cue and audible tone to signify the start of each inspiration and expiration. The separation
of inspiration or expiration allowed the $t_I/t_{Tot}$ to be set at a desired ratio. For this study this was 0.3 and 0.5.

The participants, remaining seated, followed the VEM pacing $f_R$ at 15 min$^{-1}$ and a pre-selected $t_I/t_{Tot}$ for 6 minutes. During all trials the $R_K$ device applied a constant resistance at 0.75 kPa.L.sec$^{-1}$, a level previously shown to elicit a significant response (Section 4.2). In alternate order, participants undertook trials beginning with a $t_I/t_{Tot}$ of 0.3 or 0.5. At each $t_I/t_{Tot}$ ratio participants undertook three trials with $R_K$ applied during inspiration only, expiration only or throughout both phases, with the 6 trials delivered in random order. Study parameters were calculated per breath from data (Section 3.1.6.) with the first minute of data being discarded from the analysis (Section 4.1.4).

Data analysis
For the phase loaded trials Student t-tests were used to assess for statistical differences between pre-selected $t_I/t_{Tot}$ ratio, while a one way ANOVA was used to test for differences between phase loading. When significance was identified Holms- Sidak Post-hoc testing was used. Adherence to the VEM was assessed by the number of 6-minute trials that were within ± 1 and 5 % of the target average $f_R$ and $t_I/t_{Tot}$ respectively.

4.5.3 Results
The 15 participants $f_R$ and $t_I/t_{Tot}$ at rest were 15 ± 5 min$^{-1}$, and 0.43 ± 5 respectively. These subjects completed eighty-seven trials with data being lost for three trials due to technical faults. No side effects were reported, and no trials had to be halted early by the study investigators.

In terms of $f_R$, subjects were successfully able to follow the VEM paced rate with the all trials average $f_R$ during the 6-minute trials being within 1% of target rate. However not all subjects could accurately follow the VEM paced $t_I/t_{Tot}$ ratio with only 29/45 (64%) and 29/42 (69%) participants being within ± 5% of the target $t_I/t_{Tot}$, 0.3 and 0.5 respectively (Table 4.2). These 58 successful “on-target” trials were analysed further.
Table 4.2: Trials Successfully Within ± 5% of the Target $t_i/t_{Tot}$ at Trial End.

<table>
<thead>
<tr>
<th>Target $t_i/t_{Tot}$</th>
<th>Phase Load</th>
<th>Successful/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>Inspiration</td>
<td>6/15</td>
</tr>
<tr>
<td></td>
<td>Expiration</td>
<td>12/15</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>11/15</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>29/45 (64%)</strong></td>
</tr>
<tr>
<td>0.5</td>
<td>Inspiration</td>
<td>12/13</td>
</tr>
<tr>
<td></td>
<td>Expiration</td>
<td>7/15</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>10/14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>29/42 (69%)</strong></td>
</tr>
</tbody>
</table>

The $V_{T_i}$ remained constant irrespective of phase load or imposed $t_i/t_{Tot}$ (Fig 4.8). The $W_{rs}^{mouth}$ during inspiratory-only loaded trials was significantly higher in the $t_i/t_{Tot}$ trials at 0.3 vs 0.5, at -0.59 ± 0.13 vs -0.35 ± 0.13 JL$^{-1}$ respectively (Fig 4.8). During expiratory-only loaded and combined (inspiratory and expiratory) loaded trials $W_{rs}^{mouth}$ no differences were observed between different $t_i/t_{Tot}$ (Fig 4.8). During imposed $t_i/t_{Tot}$ of 0.5 no differences were observed in $W_{rs}^{mouth}$, however at a $t_i/t_{Tot}$ of 0.3 $W_{rs}^{mouth}$ was found to be significantly higher in inspiratory versus expiratory loaded trials, -0.59 ± 0.13 vs -0.31 ± 0.10 JL respectively (fig 4.8).
Figure 4.8: (A) InWrs$^{\text{mouth}}$ (J.L) and (B) Vr$_{t_1}$ (L) During Phase Loaded Trials at $t_i/t_{\text{Tot}}$ of 0.3 (black bars) and 0.5 (grey bars). * sig diff with expiratory loaded trial.
4.5.4 Discussion

The least efficient breathing was observed when $t_I$ was shortest ($t_I/t_{Tot} = 0.3$). Participants found it most difficult to adhere to a loaded inspiratory phase (unloaded expiratory phase), whether this lack of adherence was due to the short sharp inspiration or the prolonged expiration was difficult to ascertain. Overcoming airway resistance during expiration is a design feature of the lungs as the elastic recoil of the chest wall and lungs drives flow passively.

Some participants found it difficult to adhere to the preselected $t_I/t_{Tot}$ ratios with only 58 out of the 87 trials being successfully on target. In those that were successful no observed difference between trials at 0.3 and 0.5 when loaded in both phases. It would therefore appear that controlling $t_I/t_{Tot}$ is unnecessary when applying a 6-minute test with $R_K$ load. This precludes attempting to control $t_I/t_{Tot}$ although the difficulties seen in getting participants in this study to breathe at predetermined $t_I/t_{Tot}$ illustrates how difficult this may be.

Often previous studies of respiratory endurance ask participants to follow a prescribed $t_I/t_{Tot}$ (Section 2.2.12) but then do not then report how well their technique was able to control breathing pattern. In short how well did participants adhere to any metronome used? This data shows that there is a fairly high failure rate/non-adherence. Were all trials in these previous studies analysed irrespective of how well subjects adhered to an intended $t_I/t_{Tot}$ rate or were they excluded from analysis? From the relevant sections of these studies this is unclear.

When a target $t_I/t_{Tot}$ is used it is often fixed at 0.5, which is higher than ‘normal’ resting values (i.e. 0.43 was observed in this study). This difference is probably due more to the availability of standard commercial (i.e. symmetrical) metronomes, rather than a belief that a $t_I/t_{Tot}$ of 0.5 reflects the most appropriate breathing pattern. This study indicates that attempts to control breathing pattern while applying a 6 minute sub-maximal resistive load results in an overly complex measure which requires the participant to concentrate on their breathing particularly when the $t_I/t_{Tot}$ is much lower than a subjects resting rate, a consequence of which is to increase the $\text{InWrs}_{\text{mouth}}$. Targeting the $t_I/t_{Tot}$ ratio below 0.4 while applying an inspiratory load only is the most difficult breathing pattern to adopt. A 6-minute trial using a self-controlled
breathing pattern with a constant resistance of 0.75 kPa.L.sec\(^{-1}\) applied throughout the respiratory cycle provides in healthy subjects a suitable ‘non-volitional’ method, in that no prescribed breathing style or pattern is required of a participant, of measuring InWrs\(^{\text{mouth}}\).

4.6 6-minute R\(_K\) protocol

When applying the 6-minute test using a R\(_K\) load the following protocol should be adhered to:

4.6.1 Data Analysis

The first minute of data sampling should be discounted with only that from minutes 2 – 6 being used for analysis. Data should be calculated and expressed per breath.

4.6.2 Control of Breathing Pattern

Trials should be unpaced, both f\(_R\) and t\(_I\)/t\(T_{\text{ot}}\) should be freely selected by participant. This makes the 6-minute trial protocol easy to administer in terms of instruction by an operator ‘breathe through this device in a relaxed manner for six minutes, I will tell you when to stop’ and for participants to undertake as they do not have to regulate their breathing pattern to a predetermined order. This reflects a more natural style of breathing and is closer to the overall aim of non-volitional testing of respiratory status.

4.6.3 Phase Loading

Both inspiration and expiration should be loaded as the effect on V\(T_I\) and InWrs\(^{\text{mouth}}\) was similar at different t\(_I\)/t\(T_{\text{ot}}\) ratios.

4.6.4 Level of Resistance

An R\(_K\) load of 0.75 kPa.L.sec\(^{-1}\) is a suitable load that can be applied in healthy individuals that can provoke a significant increase in InWrs\(^{\text{mouth}}\) from trials with an R\(_K\) set at 0 kPa.L.sec\(^{-1}\).

4.6.5 Outcome parameters and Pearson’s Correlation

The main effect of applying a constant resistance is the increase in the pressure generated by the respiratory system. This increased work performed against this external load, InWrs\(^{\text{mouth}}\), is able to provide sufficient information for the purposes of measuring the endurance of the respiratory system (ATS 2002\(^A\)).

A Pearson’s correlation was undertaken (Fig 4.9) to assess for any relationships between the 6-minute trial parameters and standard respiratory function tests. The
forty trials undertaken in Section 4.1 were reanalysed (40 healthy participants (31M:9F; Age range 18-64; FEV1%pred 103 ±13).

The lack of correlation between InWrs\textsuperscript{mouth} and respiratory muscle strength confirms that while there may be some interaction there is no direct relationship between strength and endurance. This provides more evidence that suggests previous techniques that have used strength based methodologies are not suitable measures of endurance.

During trials at different R\textsubscript{K}, VT\textsubscript{I} was not seen to significantly change and therefore remains stable during 6-minute seated tests. VT\textsubscript{I} was seen to correlate with height, FEV\textsubscript{1}%pred & MIP. VT\textsubscript{I}/t\textsubscript{I} correlated with height and weight.

In these healthy individuals completing a 6-minute protocol to the specifications described above (Section 4.6.1 – 4.6.4), InWrs\textsuperscript{mouth} was found to be -0.33 ± 0.08 (J.L). Therefore in individuals with poorer respiratory endurance such as patients with chest disease it would be expected that they would have an increased InWrs\textsuperscript{mouth} above this value. Loading stresses the respiratory system in a way which is similar to those imposed by chest disease and may therefore afford insight into problems of clinical relevance (Anthonisen 1976).
**Figure 4.9: Pearson’s Product Moment Correlation for 40 trials at R\(_K\) of kPa.L.sec\(^{-1}\).** [Height (M), Weight (kg), MIP (cmH\(_2\)O), \(f_R\) (bpm\(^{-1}\)), \(t_t\) (sec), \(t_E\) (sec), \(t_{TOT}\) (sec), \(W_I\) (J), \(V_{T_I}\) (L), \(W_I/t_t\) (J/sec\(^{-1}\)), \(V_{T_I}/t_t\) (L/sec\(^{-1}\)) InWrs\(^{\text{mouth}}\) (J.L)]. A correlation coefficient of 0 to 0.3 is classed as a week correlation, while between 0.3 to 0.7 signifies a moderate correlation and above 0.7 a strong correlation. *\(p<0.05\), #\(p<0.01\), **\(p<0.001\).
4.7 Summary & Future Directions

In Summary……..
In this chapter I conducted 5 individual studies of 40 healthy subjects who undertook 215, 6-minute R_K trials and of 11 subjects who completed body plethysmography manoeuvres.

The Participant
- All subjects tolerated all seated 6-minute trials, adapting to the R_K loads within the first minute and entering into a steady state breathing pattern.

The Test
- For the 6 minute R_K trial protocol, participants should be able to self select their respiratory pattern, the R_K load should be applied throughout and the first minute of data should be disregarded for analysis.
- Outcome parameters of the 6-minute trial did not correlate with standard lung function parameters although as these do not represent measures of endurance this was not surprising.

4.7.1 Future Directions for research

1. A comparison in patients with COPD would be informative as Dellwegg et al. (2008) report a marked increase in the work of breathing these patients. Can this 6-minute trial with this protocol be used to differentiate between Health and Disease?

2. VT_{I} was seen to remain constant during seated 6-minute trials, what effect does increased ventilation have on InWrs_{mouth}. The most obvious way of doing this is to use the 6-minute trial during aerobic exercise at various intensities.
Chapter 5 – Repeatability and Calibration

5.0 Introduction and Overview
5.1 RK Device Calibration
5.2 Repeatability of 6-minute Trial
5.3 Repeatability of TBPA
5.4 Summary & Conclusions

5.0 Structure and Overview

This chapter initially examines the accuracy and reliability of the RK device (Section 3.1) before assessing the biological repeatability of the 6-minute trial (Section 4.6). It then goes on to assess the reliability and repeatability of TBPA analysis (Section 3.2).

Realistically some amount of error is always present with physiological measurements and as highlighted in Section 1.6, the key to the accuracy of standard lung function tests such as spirometry is to try and minimise the degree of error to promote the most accurate result. All measurement methods employed to assess human physiology have some degree of test-retest error attributable to this natural biological variation (Atkinson & Neville 2007). Between-occasion repeatability is influenced by biological variation in lung function in addition to the stability of the measuring instrument and the technical consistency of the subject (Chan et al 2003).

Therefore the reliability of a method can be considered as the amount of measurement error that has been deemed acceptable for the effective practical use of a measurement tool. Logically it is reliability that should be tested initially in any new measurement tool, since it will never be valid if it is not adequately consistent in whatever value it indicates from repeated measurements (Atkinson & Neville 1998).

Standard deviation (SD) can be used to describe the spread of data, 2 SD either side of the mean account for 95% of data points (ARTP 2006). Additionally the accuracy of the lung function measurement can be calculated as the typical error and is best expressed as the coefficient of variation (percentage of the mean) (Hopkins 2000). The hypothesis that this chapter seeks to test is that the two techniques described previously, RK and TBPA are repeatable and reliable measures.
5.1 **RK Device Calibration**

5.1.1 **Introduction**

For a new device or approach to human physiological measurement, as detailed above it is important to establish the repeatability of such a method. Over a period of ten months (March ‘08 – December ‘09) twenty separate testing sessions were conducted during which the repeatability of the RK device calibration was assessed. The protocol used was based upon the device manufacturer’s guidelines (Micro Medical 2007).

5.1.2 **Methods**

*Pressure Calibration*

A custom built U-tube water manometer (Fig 5.1) was used to provide the inspiratory pressure required to calibrate the RK device. The calibration required a three way system in which the RK device was connected to the water manometer and a commercially available digital pressure manometer (APM130, Anton Industrial Services Ltd, UK). As all devices would be affected equally by ambient conditions (temperature and atmospheric pressure), no special considerations were made. Ambient room temperature, pressure and humidity were recorded on each occasion, the ranges were; 15-24°C; 992-1026 mmHg; 28-62% respectively.

For calibration the RK device required a constant pressure of 10 mmHg to be applied (Micro Medical 2007) equivalent to 13.2 cmH_{2}O. The U-tube water manometer was used to generate this pressure by increasing the distances between the two meniscuses by 13.2 cm. When this distance was observed it was cross referenced to the digital manometer to confirm the correct pressure had been generated. When the applied pressure load was seen to be 10mmHg it was applied to the RK device and the result recorded. (An accept button on the software ensured that the calibration was stored by the RK device).

*Flow/Volume Calibration*

A calibrated three litre syringe was used to develop inspiratory and expiratory flow as detailed in the RK device guidelines at flow rate between 1-2 L.sec^{-1}. The RK device integrates flow and time to give inspiratory and expiratory volumes which were recorded. This is a common way to calibrate flow devices as it is assumed that the relationship between flow and volume is linear.
Statistical analysis

Data was plotted for twenty separate occasions with the mean shown and ± 2 SD. Additionally the coefficient of variation was calculated as the mean divided by SD.

Figure 5.1: U-tube Water manometer and pressure calibration rig

5.1.3 Results

The coefficient of variation for inspiratory and expiratory flow, and inspiratory pressure measurements were 0.78, 0.72 and 1.48 % respectively (Figure 5.2).
Figure 5.2: (A) Expiratory Volume (L), (B) Inspiratory Volume (L) and (C) Inspiratory Pressure (mmHg) Over Twenty Separate Measurements. Solid black line = mean. Broken line ± 2 SD.

5.1.4 Discussion

The coefficients of variation were found to be less than 1.5% indicating that the $R_K$ device showed little deviation from the set values for pressure and flow. It can
therefore be confidently stated that parameters assessed by the R_K device such as InWrs\textsuperscript{mouth} can be expressed with a suitable level of reliability. This data shows that over a ten month period, and irrespective of season, the device is a trustworthy and stable measurement tool.

5.2 Biological Repeatability of 6-minute Trial

5.2.1 Introduction

The stability of the R_K device allowed the biological repeatability of the 6-minute trial to be assessed in healthy human participants. Two separate studies were undertaken; 1) to assess intra-subject variability in a single subject assessed over twenty occasions; and 2) to assess inter-participant variability between three participants measured on two occasions, six months apart.

5.2.2 Method – Intra-Participant Study

A single healthy male participant (age 32 yrs; FEV\textsubscript{1} \%pred 115) undertook twenty serial measurements over a period of ten months (Table 5.1). Measurements were conducted when the participant was in good health with no severe symptoms of any respiratory infections.

<table>
<thead>
<tr>
<th>Pulmonary Function Test</th>
<th>FEV\textsubscript{1}</th>
<th>FVC</th>
<th>MIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>R_K 6 minute trial @ 0.75 kPa.L.sec\textsuperscript{-1}</td>
<td>Unpaced seated</td>
<td>Paced seated</td>
<td>Unpaced walking on treadmill at 4 kmh\textsuperscript{-1}</td>
</tr>
</tbody>
</table>

For all 6-minute trials InWrs\textsuperscript{mouth} was used as the main outcome parameter (Section 4.6). InWrs\textsuperscript{mouth} and lung function data was plotted over twenty separate occasions with the mean \( \pm 2 \) SD shown. Additionally the coefficient of variation was calculated as mean/SD.

5.2.3 Method – Inter-Participant Study

Three healthy male participants (age range 25-46 yrs; FEV\textsubscript{1} \%pred 102-123) undertook a series of R_K trials with f_R paced and unpaced on two visits 1 week apart (Table 5.2). These trials were repeated in a similar fashion on a second occasion.
>8 months later. For all 6-minute trials InWrs\text{mouth} was used as the main outcome parameter. The mean of differences in InWrs\text{mouth} and lung function data was calculated (Table 5.2)

**Table 5.2: Measures Undertaken for Each Measurement Set (n=3)**

<table>
<thead>
<tr>
<th>Pulmonary Function Test</th>
<th>FEV$_1$</th>
<th>FVC</th>
<th>MIP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rk 6 minute trial</strong></td>
<td>Unpaced</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seated at 0 kPa.L.sec$^{-1}$</td>
<td>Seated at 0 kPa.L.sec$^{-1}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seated at 0.75 kPa.L.sec$^{-1}$</td>
<td>Seated at 0.75 kPa.L.sec$^{-1}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seated at 1.5 kPa.L.sec$^{-1}$</td>
<td>Seated at 1.5 kPa.L.sec$^{-1}$</td>
<td></td>
</tr>
<tr>
<td>Walking on treadmill at 4 kmh$^{-1}$ at 0 kPa.L.sec$^{-1}$</td>
<td>Walking on treadmill at 4 kmh$^{-1}$ at 0 kPa.L.sec$^{-1}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**5.2.4 Results – Intra-Participant Study**

The coefficient of variation for both FEV$_1$ and FVC was 2.6%, MIP showed a significant increase during the twenty trials (Fig 5.3). Coefficient of variation for InWrs\text{mouth} during 6-minute trials whilst seated with f$_R$ paced or unpaced was 20% and 7% respectively. The coefficient of variation for InWrs\text{mouth} the 6-minute trial whilst walking was 7% (Fig 5.4).
Figure 5.3: (A) FEV\textsubscript{1} (L), (B) FVC (L) and (C) MIP (cmH\textsubscript{2}0) Over Twenty Serial Measurements in a Single Participant. Panel A & B the mean (solid line) ± 2 SD (broken lines) is shown. Panel C, \(r^2 = 0.72\) p<0.001.
Figure 5.4: InWrs^mouth (J.L) During R_k Loaded Trials at 0.75 kPa.L.sec^{-1} with Breathing Unpaced (A) and Paced at 15 bpm^{-1} (B) and Unpaced While Walking on a Treadmill at 4kmh (C) Over Twenty Serial Measurements in a Single Subject. The mean (Solid line) ± 2 SD (broken line) is shown.
5.2.5 Results of Inter-Participant Study

The mean length of time between two testing occasions was 366 ± 175 days. The small study size dictates that it is difficult to apply meaningful statistical testing. However the mean difference in the spirometric measurements show a variation of less than 100 ml (Table 5.3) over a period of more than six months which is below the maximal 150ml difference described in testing guidelines (BTS 1994) as necessary for reliable testing of spirometry on a single occasion. Mean differences in InWrs\textsuperscript{mouth} during 6-minute trials appear to be higher and more variable (in terms of larger SD) when fr is paced rather than unpaced (Table 5.3).

| Table 5.3: Mean and SD of Differences in Spirometry and InWrs\textsuperscript{mouth} (J.L) |
|------------------|------------------|------------------|
| Spirometry       | Best FEV\textsubscript{1} (L) | 0.090 | 0.090 |
|                  | Best FVC (L)     | 0.013 | 0.235 |
| InWrs\textsuperscript{mouth} (J.L) | Paced fr Trials |                     |      |
| R\textsubscript{k} Load | 0 kPa.L.sec\textsuperscript{-1} | 0.12 | 0.20 |
|                  | 0.75 kPa.L.sec\textsuperscript{-1} | 0.18 | 0.31 |
|                  | 1.5 kPa.L.sec\textsuperscript{-1} | 0.80 | 1.39 |
|                  | 0 kPa.L.sec\textsuperscript{-1} at 4kmh walk | 0.24 | 0.49 |
| Unpaced fr Trials |                     |      |      |
| R\textsubscript{k} Load | 0 kPa.L.sec\textsuperscript{-1} | 0.05 | 0.05 |
|                  | 0.75 kPa.L.sec\textsuperscript{-1} | 0.10 | 0.04 |
|                  | 1.5 kPa.L.sec\textsuperscript{-1} | -0.03 | 0.10 |
|                  | 0 kPa.L.sec\textsuperscript{-1} at 4kmh walk | 0.09 | 0.05 |

5.2.6 Discussion

Spirometry Variability

In the intra-participant study the coefficient of variation of FEV\textsubscript{1} and FVC, while higher than that described for the repeatability of the R\textsubscript{k} device, is still less than 2.5%, indicating that spirometry as expected is a reliable measure. Furthermore the mean difference of less than 150ml in both FEV\textsubscript{1} and FVC when assessed over a period of more than eight months indicates that both are stable measurements in healthy individuals.
6-minute Trial – InWrs\textsuperscript{mouth} Variability

The coefficient of variation for R\textsubscript{K} trials in the subject study when \( f_{R} \) was unpaced was lower than that observed in paced trials, additionally the mean InWrs\textsuperscript{mouth} during seated paced R\textsubscript{K} trials was significantly higher than during unpaced trials. This increased average difference in InWrs\textsuperscript{mouth} during \( f_{R} \) paced 6-minute trials was replicated in the inter-participant study. This shows how conscious control over breathing increases trial outcome and confirms other data collected during the development of the 6-minute protocol (described in Section 4.6) which requires breathing to be unpaced during 6-minute trial.

The coefficient of variation for unpaced seated R\textsubscript{K} trial protocol was higher than that seen in FEV\textsubscript{1} and FVC. However it can still be confident in the assessment of InWrs\textsuperscript{mouth} as a 7% variation in the mean value of InWrs\textsuperscript{mouth} in healthy participants of 0.33(J.L) (Section 4.6) would be equivalent to a range of 0.31-0.35 (J.L). Therefore any changes greater than 0.02 (JL) would be measurable. MIP was found to significantly increase over the training period. This perhaps shows the learning or training effect that is influenced by repeated respiratory testing?

5.3 R\textsubscript{K} Device – In Conclusion

Standard spirometric testing (Section 3.4) as would be expected showed good repeatability and is a useful and robust measure with which to compare the R\textsubscript{K} device. This data shows that the R\textsubscript{K} device is both consistent and reliable, and provides a repeatable and stable measure of InWrs\textsuperscript{mouth} in human participant.

Although these small studies indicate the reliability and repeatability of the R\textsubscript{K} device it would be useful to expand such repeated testing in a greater number of both male and female participants, and in relevance to the studies described later in this thesis in patients with chest disease. At this point in time (November 2009) no other group has published repeatability data for this device.
5.4 Reliability of TBPA in Control Participants

5.4.1 Introduction
The aim of this study was to assess the tidal airflow profile analysis equations developed by Colsanti et al 2004 (Section 3.2.1), as an alternate measure of airway obstruction, as FEV$_{\text{TAP}}$, in healthy controls.

5.4.2 Methods
Fifty (34M:16F) healthy controls (Age range 18-48 yrs; FEV$_1$ %pred 103 ± 12) were asked whilst seated and relaxed to breath through a pneumotachograph for 3 minutes. FEV$_{\text{TAP}}$ was derived using equation described previously (Section 3.2.1): FEV$_{\text{TAP}}$ = -5.41 + (Height x 4.97) + (Age x -0.02) +(t$_{\text{PTEF}}$ x 0.005). Standard spirometric measurement (Section 3.4) provided the directly measured FEV$_1$ with which FEV$_{\text{TAP}}$ was compared. Linear regression was used to assess for relationship between FEV$_1$ and FEV$_{\text{TAP}}$, and the difference between FEV$_1$ and FEV$_{\text{TAP}}$ was also calculated.

5.4.3 Results
The three minutes of resting breathing was well tolerated by all participants and all trials were completed successfully. The average resting $f_R$ was found to be 16±4 bpm$^{-1}$. FEV$_{\text{TAP}}$ was seen to correlate with FEV$_1$ (Fig 5.5) but slightly over-predicted FEV$_1$ (0.123ml) (Fig 5.6).

5.4.4 Discussion
In healthy controls FEV$_{\text{TAP}}$ can be used to provide a surrogate measure of FEV$_1$. Although FEV$_{\text{TAP}}$ over predicts FEV$_1$ observed difference is still less than 150 ml in a similar manner to the differences in spirometry observed previously (Section 5.2.6). TBPA may not be as sensitive as spirometry but shows similar reliability.
Figure 5.5. Relationship Between FEV\textsubscript{1TAP} and FEV\textsubscript{1} in Healthy Controls. Line of best fit ($r^2 0.57 \ p<0.001$) is shown with 95% prediction.

Figure 5.6: The Difference Between FEV\textsubscript{1TAP} and FEV\textsubscript{1} for Healthy Controls:
The mean $\pm$ 2 SD is shown.
5.5  **Repeatability of TBPA in Healthy Controls**

In a similar manner to the studies undertaken with the Rk device (Section 5.2) further investigations were undertaken in control participants to assess the repeatability of TBPA. Three separate studies were undertaken, to assess intra- participant variability in one participant, and intra- participant variability over many occasions (n=6) and within occasion (n=11).

5.5.1  **Method – Intra-Participant Study n=1**

A healthy male participant (age 32; FEV₁ %pred 115) made twenty serial TBPA measurements. Using formula previously described (Section 3.2) FEV₁TAP was calculated and compared with sequential measurements and directly measured FEV₁ (Section 3.4). Data was plotted as twenty separate occasions with the mean shown and +/- 2 SD. Additionally the coefficient of variation was calculated as mean divided by SD.

5.5.2  **Method – Inter Participants Study**

Six healthy participants (4M:2F age range 22-36; FEV₁ %pred 97-128) completed serial measurements over eight consecutive weeks. Using formula previously described (Section 3.2) FEV₁TAP was calculated and compared with sequential measurements and directly measured FEV₁ (Section 3.4). A one way repeated measures ANOVA was used to assess for difference between measurements.

5.5.3  **Intra Participants Study n=11**

Eleven healthy male participants (Age range 18-29; FEV₁ %pred 99% ± 14) completed three spirometric and TBPA measurements over two occasions (one week apart), one on first visit and two on a second visit separated by approximately 20-minutes.

Using formula previously described (Section 3.2) FEV₁TAP was calculated and compared with sequential measurements and directly measured FEV₁ (Section 3.4). A 2-way repeated measure ANOVA was used to assess for difference between measurements.

5.5.4  **Results - Single Participants**

All manoeuvres were well tolerated and were successfully completed. FEV₁TAP was significantly lower than directly measured FEV₁, 3.9 ± 0.1 and 4.7 ± 0.4 respectively. However FEV₁TAP had a lower coefficient of variation than directly measured FEV₁, 2.6% and 3% respectively (Fig 5.7).
5.5.5 Results - Six Participants

TBPA manoeuvres were well tolerated by all six subjects and were successfully completed. Both FEV\textsubscript{ITAP} and directly measured FEV\textsubscript{1} were not significantly different and did not change over time (Fig 5.8).
5.5.6 Results - Eleven Participants

The TBPA trials were tolerated well by all eleven participants and all were successfully completed. FEV$_{1TAP}$ was seen to correlate with FEV$_1$ ($r^2$ 0.52 $p<0.001$) in a similar way to that reported earlier ($r^2$ 0.57 $p<0.001$; Section 5.4.3). There were no significant differences between FEV$_{1TAP}$ and FEV$_1$. Both FEV$_{1TAP}$ and FEV$_1$ were stable with no statistical difference found between the three measurement occasions (1$^{st}$, 2ndA and 2ndB) (Table 5.4). Additionally there were no statistical differences between FEV$_{1TAP}$ and FEV$_1$. 

Figure 5.8: Serial (A) FEV$_{1TAP}$ (L) and (B) Directly Measured FEV$_1$ (L) in Six Participants Over Eight Consecutive Weeks.
Table 5.4: Directly Measured FEV\textsubscript{1} and FEV\textsubscript{1TAP} in 11 Healthy Males (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>1st Visit</th>
<th>2nd Visit A</th>
<th>2nd Visit B</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV\textsubscript{1TAP} (L)</td>
<td>4.26 (0.52)</td>
<td>4.28 (0.55)</td>
<td>4.18 (0.59)</td>
</tr>
<tr>
<td>FEV\textsubscript{1} (L)</td>
<td>4.34 (0.84)</td>
<td>4.40 (0.82)</td>
<td>4.34 (L)</td>
</tr>
</tbody>
</table>

5.5.7 Discussion

This study has shown that in each of the three sub studies FEV\textsubscript{1TAP} was repeatable and a good surrogate measure for FEV\textsubscript{1}.

5.6 Summary & Conclusions

In Summary…….

In this chapter I conducted 6 studies with 4 participants completing 108 6-minute R\textsubscript{K} trials and 68 participants completing 143 TBPA trials.

The Participant

- Participants were able to complete all R\textsubscript{K} and TBPA trials and reported no adverse effects.

The Test

- Standard lung function was seen to be the most reliable measure with the smallest coefficient of variation.
- R\textsubscript{K} trials when f\textsubscript{R} was unpaced showed lower coefficient of variation than when f\textsubscript{R} was paced.
- R\textsubscript{K} and TBPA trials are both reliable and reproducible measures.

This data shows that in healthy participants TBPA and R\textsubscript{K} trials are reliable and reproducible measurements using the protocols described in Chapters 3 and 4, confirming the hypothesis set out in section 5.0. As the subsequent work of this thesis examines the use of these methods in clinical groups, patients with chest disease and children it would be a valuable exercise to undertake similar studies of the repeatability and reliability of the techniques in these groups.
Chapter 6 – Work of Breathing and Exercise

6.0 Introduction & Overview

This chapter examines the effect of increased ventilation during 6-minute trials and the effect on $\text{InW}_{\text{Rs}^\text{mouth}}$ by asking participants to complete trials whilst exercising. Initially the intensity of exercise was low so the effect could be controlled, however as studies and trials were successfully undertaken the intensity of exercise and the level of $R_K$ applied during trials was increased.

Physical exercise induces increases in ventilation that requires extra work to be performed by the respiratory system. The appropriateness of the ventilatory response to exercise depends not simply on the level of ventilation required for a particular work rate but also to the extent that it is able to maintain pulmonary gas exchange and acid base control of respiration (Whipp et al 2007). The lung parenchyma and airways are ‘built’ in healthy adults to handle these challenges of the increased gas exchange demanded during exercise (Dempsey 2006$^A$) and during high intensity exercise ventilation can increase by twenty fold from resting levels (Guenette & Sheel 2007). In general the functional capacity of the healthy respiratory system exceeds the demands placed upon it, although it has been hypothesised that at high intensity there is a respiratory muscle fatigue metaboreflex causing reduced blood flow to locomotor muscles (see review by Dempsey et al 2006$^B$).

Exercise intolerance is a consequence of an individual’s inability to meet the physiological requirements of a particular task (Whipp et al 2007). It has become clear that the diaphragm, like other skeletal muscle is susceptible to fatigue with heavy whole body dynamic exercise (Johnson et al 1996$^B$). At lower sub-maximal levels of exercise intensities which do not result in fatigue, the capacity of the respiratory system in healthy individuals should not be exceeded. However the work of breathing increases secondary to increases in both lung and chest wall elastic recoil and airway resistance during even moderate exercise (Cloutier 2007).
This chapter aims to define the relationship between ventilation and \( \text{InWrs}^{\text{mouth}} \) during sub-maximal exercise in participants completing a 6-minute \( R_K \) protocol (Section 4.6) at different levels of \( R_K \) and exercise intensity. The hypothesis that chapter seeks to test is that increases in ventilation due to exercise result in increases in \( \text{InWrs}^{\text{mouth}} \).

6.1 Methods

To create a variety of ventilation rates and exercise modalities three groups of participants each underwent a different test protocol on single visits to the laboratory. In total forty-five healthy participants took part, (Table 6.1) upon gaining consent, body weight and height were taken and baseline spirometry measured (Section 3.4.1). These participants completed 6-minute \( R_K \) trials while undertaking steady state exercise protocols. The repeatability of the 6-minute trial whilst exercising has already been established (Section 5.2).

<table>
<thead>
<tr>
<th>Table 6.1: Participant Demographics for Three Exercise Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol 1 N=10</td>
</tr>
<tr>
<td>Sex (M:F)</td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>FEV(_1 )%predicted</td>
</tr>
<tr>
<td>MIP (cm H(_2)O)</td>
</tr>
</tbody>
</table>

**Exercise Protocol One**

Ten participants were asked to complete two 6-minute trials with \( R_K \) set at 0 kPa.L.sec\(^{-1}\), once while seated and again while walking on a treadmill at 4 km.h\(^{-1}\) (equivalent to 2.5 mph\(^{-1}\)). This locomotion speed was selected as it was at an intensity that best reflected an average walking speed in healthy individuals.

**Exercise Protocol Two**

Twenty participants completed four trials, two seated and two exercise trials at \( R_K \) loads of 0.75 and 1.5 kPa.L.sec\(^{-1}\) similar to studies described previously (Chapter 4). \( f_R \) was paced using an electronic metronome (Section 3.3) and set at 15 min\(^{-1}\). Ten participants completed exercise tests on a treadmill at 4 km.h\(^{-1}\) and the remaining ten completed exercise tests on a cycle ergometer loaded at 50 Watts.
Exercise Protocol Three

Fifteen participants completed five trials, three seated at 0, 0.75 and 1.5 kPa.L.sec\(^{-1}\) and two exercise trials at 100 and 150 Watts with an \(R_k\) load of 0.75 kPa.L.sec\(^{-1}\). The exercise trials were modified Astrand Rhyming cycle trials (Section 3.5.2) and were used to select suitable exercise work loads. Additionally as with the Astrand Rhyming protocol, participants only completed the 150 Watt trial if their \(f_H\) during the 100 watt trial did not exceed a set \(f_H\), for this study this was set at 130 min\(^{-1}\).

Statistical Analysis

For each 6-minute trial InWrs\(^{\text{mouth}}\) and \(V_e\) were calculated and expressed per breath. Linear regression was used to assess for relationships between parameters and derived using statistical software (SigmaPlot V11, Systat, UK).

6.2 Results

Participants tolerated all seated trials during the three exercise protocols, successfully completing ninety-five trials with none ending early. For protocol one, all exercise trials were successfully completed. For protocol two, four exercise trials were not completed, three because participants could not maintain ventilation through the device and one due to technical reasons. In protocol three, all 100 Watt exercise trials were successfully completed. Eight participants had a \(f_H \leq 130\) min\(^{-1}\) and successfully undertook all 150 Watt trials.

Irrespective of breathing pattern (paced or unpaced) or exercise mode, \(V_e\) was seen to increase with InWrs\(^{\text{mouth}}\) in a linear fashion (Fig 6.1). The slope of this relationship was steeper as the load was increased, at 0.02, 0.033, and 0.064 J.L for each litre increase in \(V_e\) at loads 0, 0.75 and 1.5 kPaLsec\(^{-1}\) respectively. The combined data was used to construct isopleths for each five litres of ventilation (Fig 6.2). This illustrates that at low resistive loads (as found in the healthy airway) InWrs\(^{\text{mouth}}\) may triple with a four-fold increase in ventilation (10-40 L.min\(^{-1}\)), (Point A, Fig 6.2), while in the presence of high loads the same increases in ventilation evoke an almost five-fold increase in InWrs\(^{\text{mouth}}\) (Point B, Fig 6.2). No relationship (\(p >0.05\)) between MIP and InWrs\(^{\text{mouth}}\) was observed.
Figure 6.1: Relationship Between $\dot{V}_E$ (L.min$^{-1}$) and InWrs$^{\text{mouth}}$ (J.L) at Increasing $R_K$ (kPa.L.$\text{sec}^{-1}$). Applied load was 0 (grey fill), 0.75 (black fill) and 1.5 (no fill) kPa.L.$\text{sec}^{-1}$. Exercise Modes; Circles, seated; squares, walking at 4 kmh$^{-1}$; diamonds, cycling at 50 watts; triangles, at 100 watts; stars, at 150 watts. Fitted linear regression are shown for each applied load, $r^2 = 0.85, 0.93, 0.93$, all $p < 0.001$, at 0, 0.75, 1.5 kPa.L.$\text{sec}^{-1}$ respectively.

Figure 6.2: Exponential Relationship Between $R_K$ (kPa.L.$\text{sec}^{-1}$) and InWrs$^{\text{mouth}}$ (J.L) at Increasing $\dot{V}_E$ (L.min$^{-1}$)
6.3 Summary & Conclusion

In Summary……..

In this chapter I conducted 3 individual studies of 45 healthy subjects who successfully undertook 95 seated 6-minute trials and a further 69 trials whilst exercising at various $R_K$ load and increasing exercising intensities.

1. The Participant

- When breathing pattern is self-selected participants are able to complete 6-minute trials while exercising at intensities up to 150 watts, and $R_K$ loads of 1.5 kPa.L.sec$^{-1}$.

2. The Test

- Irrespective of the pattern of breathing or exercise mode, $V_E$ increases with $\text{InWrs}^\text{mouth}$ in a linear fashion dependent on the $R_K$ load applied, confirming hypothesis set out in section 6.0.
- The $R_K$ device is able to maintain $R_K$ load irrespective of $V_E$.
- $\text{InWrs}^\text{mouth}$ increases exponentially with $R_K$, implying that at higher $R_{AW}$ exercise becomes limited because of a reduced respiratory endurance rather than lack of respiratory muscle strength.

When breathing against resistance, mechanisms of load compensation induce adaptations in the pattern of breathing proportional to the applied load (Calabrese et al. 1998) and these changes act to maintain ventilation at the most optimum or efficient level (Zechman et al. 1957). The control of breathing has evolved into a highly sophisticated, negative feedback system which is able to accurately match the level of ventilation with the requirements of the body. Individuals appear to select one particular breathing pattern among the infinite number of possible combinations of ventilatory variables and airflow profiles (Benchetrit 2000) that enables the work of breathing to be minimised (Cloutier 2007). This process is an automatic unconscious one, in that individuals will find the most efficient breathing pattern for the ventilation level required. Even with additional stress such as with exercise or in disease, if this is not immediately fatiguing and remains constant, the respiratory control system will adopt the most efficient pattern of breathing.

The exercise studies focused on $R_K$ loads of 0.75 kPa.L.sec$^{-1}$ as it had become the established load for the 6-minute trial (Section 4.6). It would be a useful to see what affect the increased
exercise intensities had at the $R_K$ loads not studied (0 & 1.5 kPa.L.sec$^{-1}$), although the exponential relationship identified (Fig 6.2) would suggest that participants would struggle to complete high intensity exercise trials at high $R_K$ loads. At higher loads the $InWR_{s\text{mouth}}$ soon becomes overpowering and few subjects feel comfortable exercising while their breathing is restricted. Physiologically there is an upper limit to the tolerable resistive load during exercise before fatigue or task failure occurs. From the data it would be expected that at 2 kPa.L.sec$^{-1}$ $InWR_{s\text{mouth}}$ would become inhibitive at even moderate ventilation rates (> 30 L sec$^{-1}$). Whether the ability to overcome a high $R_K$ load is dependent on fitness levels (and motivation) or dependent upon inherent respiratory function has yet to be investigated. The effect of increased resistive load on exercise is important in individuals with increased intrinsic airway resistance ($R_{AW}$) such as asthmatics, as even small increases in $R_{AW}$ would appear to result in large increases in $InWR_{s\text{mouth}}$, which can affect their endurance capabilities.

The efficacy of respiratory training devices that apply respiratory loads are often evaluated on how they increase respiratory muscle strength, but the focus should be on improvements in respiratory endurance, as this would provide a better measure of the ability to tolerate increased $InWR_{s\text{mouth}}$. These studies indicate that the $R_K$ device is able to maintain an $R_K$ load irrespective of the level of ventilation or breathing pattern, either imposed or self selected. This would suggest that the device is able to maintain an $R_K$ load irrespective of the level of ventilation or breathing pattern, either imposed or self selected. Suggesting that as the manufacturers describe, irrespective of how individuals breathe through the $R_K$ device the applied load remains constant.

Though in healthy humans there are only a few occasions when the reserve of respiratory muscle function is utilised sufficiently to cause fatigue, there are certain groups of patients where the endurance properties of the respiratory muscles may be critical to survival or necessary for adequate exercise tolerance (Clanton and Diaz 1995). With the increased use of pulmonary rehabilitation programmes it is necessary to monitor endurance performance rather than strength, valid measures of endurance are thus needed to assess the outcomes of such interventions (Powell and Williams 2009). Despite intense investigation the importance of respiratory muscle endurance in the failing patient or the obstructed patient during exercise is still relatively inadequate. Just as important are the development of better techniques for evaluating respiratory muscle endurance and work capacity in chest disease patients (Clanton 1995).
In conclusion at a constant airway resistance, $\text{InWrs}^{\text{mouth}}$ is dependent on ventilation rate and independent of exercise modality. The $\text{InWrs}^{\text{mouth}}$ increases exponentially with resistance, which implies that at higher airway resistances exercise becomes limited because of a reduced respiratory endurance rather than lack of respiratory muscle strength.
Chapter 7 – Chronic Obstructive Pulmonary Disease

7.0 Introduction and Overview

This chapter begins with the description of the pathophysiology of Chronic Obstructive Pulmonary Disease (COPD) and how it impacts on society nationally and locally in Rhonda Cynon Taf where the clinical trials described took place. It then goes on to describe the procedures involved in designing and securing regulatory approval for these clinical trials. The assessment of InWrs\textsuperscript{mouth} and TBPA in COPD patients is then outlined, followed by the description of specific studies that took place. The experimental work in this chapter seeks to test the hypothesis that TBPA and R\textsubscript{K} trials can differentiate between COPD patients and healthy individuals.

7.1 Overview of COPD

It is an inevitable consequence of aging that humans will experience a gradual decline in lung function throughout life. On average healthy non-smoking men can expect to lose from their FEV\textsubscript{1} 23.7 ml/yr at age 25 to 39.0 ml/yr at age 75 (Ware et al 1990). Fletcher & Peto (1977) elegantly showed not only this gradual decline but also how it can be accelerated by tobacco smoking (Fig 7.1). It is now accepted that COPD is predominantly caused by prolonged tobacco smoking. Obstructive diseases are characterised by airflow limitation and obstruction, and include, asthma, chronic bronchitis and emphysema (ARTP 2006) and the recognition that COPD has both airway and airspace characteristics has led to the common definition of the disease (Shapiro & Ingentio 2005).

The most recent GOLD (2008) statement defines COPD as:
‘a treatable and preventable disease with some significant extra pulmonary effects that may contribute to the severity in some individuals. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to gases or noxious particles’.

It is estimated that COPD affects 3 million people and kills over 30 000 in the UK each year (Chief Medical Officer 2004). Acute exacerbations of COPD are a significant cause of morbidity and mortality, and are acute inflammatory events superimposed on the chronic inflammatory characteristic of COPD (Anzueto 2009). As COPD severity increases, daily activities can become very difficult. Patients with COPD can get anxious about their breathlessness and as a result reduce their levels of physical activity in order to avoid becoming breathless resulting in physical de-conditioning. This in addition to the progressive nature of COPD contributes to a ‘Spiral of Decline’ (Jones 2009) resulting in patients suffering from increasingly severe attacks of breathlessness that can leave them housebound or result in repeated extended hospital admissions. This activity limitation acts to impair these patients’ quality of life by restricting their interactions with their environment (Roche 2009) and as such invalidism should be discouraged, with exercise programs directed at increasing exercise tolerance used to help treat these patients (Rankin & Dempsey 1967).

Figure 7.1: Risk of Smoking in Men – Fletcher & Peto (1977)
7.1.2 Tobacco Smoking as a Cause of COPD

While there is little doubt that tobacco smoke is causal for the development of COPD there is a great variability in lung function among smokers and not all smokers develop COPD (Shapiro & Ingentio 2005). It is well known that if tobacco smoking was abolished, the widespread occurrence of COPD would gradually disappear and it would become a rare disease (Siafakas 2006). Tobacco smoke contains at least 69 carcinogenic compounds and many other chemical compounds including nicotine the constituent associated with the addiction that makes tobacco smoking difficult for smokers to quit (Cancer UK 2009). Tobacco smoking had three major effects; impairment of ciliary movement, mucous gland hypertrophy and altered structure and function of alveolar macrophages.

7.1.3 Pathology of COPD

Pathological changes characteristic of COPD are found in the central airways, peripheral airways, lung parenchyma and pulmonary vasculature (GOLD 2008). The heterogeneous nature of COPD is due to differing contributions of airway (chronic bronchitis) and parenchymal lung disease (emphysema) (ARTP 2006) and has been extensively reviewed elsewhere (Shapiro & Ingentio 2005: Rodriguez-Roisin & MacNee 2006). The primary cause of airway obstruction, regardless of aetiology is increased airway resistance ($R_{AW}$).

Chronic bronchitis is defined clinically as a persistent cough with sputum production for at least 3 months of the year for 2 consecutive years. As cigarette smoking affects both the production and clearance of mucous (Section 7.2) increased pools of mucous occur in the airways increasing susceptibility to infection and producing a productive cough.

Emphysema is a destructive process that results in the destruction of the alveolar walls reducing the surface area for gas exchange and increasing airflow obstruction. As alveolar tissue is naturally elastic helping to maintain the small airways, in emphysema this support is lost and the airways become narrowed (Booker 2008).

Increased levels of inflammatory cells and cytokines induce airway secretions, bronchospasm and mucosal oedema, which in turn lead to a worsening ventilation/perfusion mismatch and hyperinflation resulting in acute changes in a
patients symptoms (Anzueto 2009). As such COPD patients must generate increased $\dot{V}_E$ to maintain respiratory homeostasis when compared to healthy subjects (Jolley & Moxham 2009). Currently clinical therapies for treating COPD exacerbations include oral corticosteroids, antibiotics and bronchodilators however they appear to have only limited beneficial affects (Torres 2009).

Figure 7.2: Effect of COPD on the Structure of the Lung (from Shapiro & Ingenito 2005)

7.1.4 Diagnosis of COPD

Demonstration of the presence of airflow obstruction is necessary when making the diagnosis of COPD. Spirometry is the only accurate method of measuring the airflow obstruction in patients with COPD (NCCC. 2004). A diagnosis of COPD should be considered in individuals over the age of 35 who smoke tobacco and present with
symptoms of exertional breathlessness, chronic cough, regular sputum production or wheeze. Other risk factors include environmental exposure to noxious particles such as air pollution associated with the burning of wood or other biomass fuels (GOLD 2008). COPD is most probably the result of an interaction between these risk factors and environmental exposure. The degree of certainty of any one risk factor in COPD pathogenesis varies, however the deficiency of alpha1-antitrypsin as a factor and tobacco smoke as an exposure has been well documented (Siafakas 2006). COPD is heterogeneous and as such no single measure can give an adequate assessment of the true severity of the disease in an individual patient (NCCC 2004).

Airflow obstruction is defined as a reduced FEV₁ and FEV₁/FVC ratio such that FEV₁ is less than 80% predicted and FEV₁/FVC is less than 0.7. GOLD (2008) have further classified the progressive severity of COPD (Table 7.1).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>I: Mild COPD</td>
<td>FEV₁/FVC &lt; 0.7</td>
</tr>
<tr>
<td></td>
<td>FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td>II: Moderate COPD</td>
<td>FEV₁/FVC &lt; 0.7</td>
</tr>
<tr>
<td></td>
<td>50% &lt; FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td>III: Severe COPD</td>
<td>FEV₁/FVC &lt; 0.7</td>
</tr>
<tr>
<td></td>
<td>30% &lt; FEV₁ &lt; 50% predicted</td>
</tr>
<tr>
<td>IV: Very Severe COPD</td>
<td>FEV₁/FVC &lt; 0.7</td>
</tr>
<tr>
<td></td>
<td>FEV₁ &lt; 30% predicted or FEV₁ &lt; 50% predicted plus</td>
</tr>
<tr>
<td></td>
<td>chronic respiratory failure</td>
</tr>
</tbody>
</table>

7.1.5 Burden of Obstructive Chest Disease

Monitoring COPD in the population is a priority as it informs both healthcare policy and patient treatment. The growing burden of COPD on patients, the NHS and the economy, both locally and nationally, is seen as important and is increasingly recognised, resulting in development of national disease management guidelines (NCCCC. 2004). In the European Union, the total direct costs of respiratory disease are estimated to be about 6% of the total health care budget with COPD accounting for €38.6 billion (GOLD 2008). This may be an underestimation of the problem as
under-reporting of this healthcare burden has been identified by several recent studies (Enright 2008; Nacul et al 2007).

There are 900 000 diagnosed cases of COPD in the UK although this is widely recognised as an underestimate with the truer figure estimated to be around 1.5 million (NCCC. 2004). Approximately 30 000 people die prematurely from COPD annually in the UK (BTS. 2006). COPD is not usually detected in smokers until more than half of their lung function has been irretrievably lost and frequently not until a severe exacerbation causes hospitalisation (Enright 2008).

Estimated UK prevalence of COPD is 5.3 per cent in over 45 year olds (Nacul et al. 2007). The General Household Survey records that self-reported diagnoses of chronic bronchitis and emphysema are far lower than the prevalence values from the Health Survey for England 1996, indicating that much of the early disease is unrecognised. (LAIA. 2003). Some of the highest standardised mortality ratios are seen in South Wales (Fig 7.3) at over 130% (LAIA. 1996). The burden of COPD on patients, the health service and the economy is important and increasingly recognised, resulting in national disease management guidelines (Booker. 2008).

In addition GP consultation rates for respiratory disease are over three times as high as disease of the circulatory or digestive systems (Chief Medical Officer 2004). Around 12 % of COPD patients had visited hospital A&E departments at least once during the previous year because of COPD (Britton 2003).

_Spirometry in General Practice_

Recently there has been a lot of interest in the wider clinical literature about spirometric testing in General Practice. Recent studies have shown that 1) the prevalence and under diagnosis of COPD in adult patients in primary care make case finding worthwhile (Bednarek 2008), and 2) that opportunistic spirometry led to a higher proportion of the population at risk of developing COPD, being identified and treated, than just standard GP testing alone (Walters et al. 2008). Most COPD patients with exacerbations can be managed at home, although some do need to be hospitalised, however many patients with exacerbations often delay presentation or do not seek therapy (Torres 2009). Early treatment of COPD may help to control
symptoms, reduce the impact of exacerbations and improve quality of life (Britton 2003).

Figure 7.3: Age-Standardised Mortality Rates for Respiratory Diseases by Local Authority, Males all Ages United Kingdom 1993-1997 (Office National Statistics 2001)

FEV_{1} measurements although used to define COPD progression correlate poorly with the presence of some symptoms and therefore new strategies for managing COPD patients and their disease symptoms are required (Lacoma et al 2009). The more severe COPD becomes the more difficult it becomes to make lung function measurements as, patients get older, suffer from comorbidities and from frequent exacerbations. Even if patients cooperate, current lung function guidelines often label measurements as low quality and not good enough for assessment, meaning the patients most at risk are the hardest to assess (Soriano & Miravitllies 2009).
The diagnosis and treatment of COPD in primary care needs to be improved (Britton 2003). Maybe the holy grail of giving antibiotics only to those who benefit is not achievable using simple clinical markers (Woodhead 2009) and requires a more sophisticated approach. Could the use of TBPA in particular be useful as a means to monitor respiratory function in a primary care or home setting?

7.2 Chest Disease in Rhonda Cynon Taf: Merthyr Tydfil Breathe Easy Meeting

7.2.1 Background

Breathe Easy is part of the work of the British Lung Foundation and is a network of groups that aim to provide support and information to those people living with a lung condition and also the people that care for them (http://www.lunguk.org/supporting-you/breathe-easy/). As such they provide a valuable opportunity to communicate with a group of patients and their carers within the local community. In Rhonda Cynon Taff this is particularly relevant as the rates of mortality due to chest diseases are some of the highest in the UK (Section 7.1.5). The groups are structured to provide a social meeting place for patients with chest disease outside a clinical setting and include some form of educative process involving a weekly guest speaker.

By the end of the first year of my PhD studies I was beginning to prepare clinical studies that would involve recruiting groups of patients with chest disease. I felt that it was important that I communicated with such individuals to inform them of my work and to ask them their views about this, chest disease and clinical research in general.

I had specific questions that I was keen to answer. Did they think that it was important for research into their lung condition to be carried out? How easy/hard did they find standard spirometry to complete? Would they be willing to take part in research if approached? What about if they had just been admitted to hospital, would that willingness change? What about the minimum 24 hour rule of informed consent?

I approached the chair of the British Lung Foundation in Wales explaining my situation and that I would like offer my services as a guest speaker, describing my own and the wider research, and to ask the group some questions that may help my work. She responded positively and put me in touch with the local Chronic Disease Nurse who invited me to a Breathe Easy meeting.
7.2.2 The Meeting
I attended the weekly meeting of the Merthyr Tydfil Breath Easy group at a local community centre. After the announcements, information and raffle, I was given the opportunity to speak. I used a simple presentation to describe the ideas I wanted to discuss and handed out a short questionnaire (Appendix 7.1).

7.2.3 Results of Discussion and Questionnaire
Of the 11 people attending the meeting 8 people successfully completed the questionnaire. The main findings from this were:

1. Those present wanted to learn about research taking place.
2. The majority were happy about being asked to take part.
3. They all reported that they found spirometry hard to undertake.

7.2.4 On Reflection
I found the meeting a really positive experience, meeting the group members was very interesting and enjoyable and quite a sociable experience in itself, perhaps as the groups were originally set out to be? As a researcher it was affirming to see that those attending were interested in current research, particularly that which involved aspects of their disease. There was also a strong altruistic sense though, many of those present wanted to ‘put something back’ and a common theme was the feeling that it was their duty to assist or take part in future research. It would be interesting to see how they would feel about becoming more involved in guiding research, for example from planning new research to actively taking on researcher type roles such as user driven? There is a strong focus currently by the research councils and other funding bodies to increase the involvement of patients not as participants or subjects of research but becoming actively involved in the research process (National Patient Safety Agency 2009). In the context of chest disease and COPD, the Breathe Easy meetings provide an excellent opportunity for this.

In conclusion I got a lot out of the experience, not only information that I thought would be useful (which was perhaps what drove my interest initially) but it also made me appreciate the need to interact with the local population I was studying.

7.3 Clinical Trials Set Up
Through the Breath Easy meeting, contact was made with a Respiratory Physiotherapist at a local hospital who co-ordinates the pulmonary rehabilitation
programme. Links were also developed with a consultant physician who specialised in respiratory medicine. Collaboratively three clinical trials were set up where I acted as study coordinator and was responsible for designing the study, drafting a protocol and study documents, and getting regulatory approval for each study. This included getting approval from University of Glamorgan Faculty Ethics Committee, the local NHS Trusts Research Department and the Local Research Ethics Committee (LREC). I was able to use the feedback that I collected from the Breathe Easy meeting as user generated involvement which was a powerful support to the applications that were made to the relevant ethics committees. An example of a study protocol that I created for one of these clinical trials can be seen in Appendix 7.2.

I was responsible for conducting each study, recruiting participants and carrying out study measurements. As such on average during the final year of my PhD I attended the Royal Glamorgan and Prince Charles Hospitals for 3 clinical half day sessions per week which resulted in 56 patients being recruited.
7.4 COPD Work of Breathing Study

7.4.1 Introduction
The function of the respiratory muscles is impaired in COPD patients. The reasons for this include increased resistive and elastic loads, lung hyperinflation and less favourable length tension relation of the respiratory muscles and as a result, drive to the inspiratory muscles increases in COPD (McKenzie et al 2009). As the mechanical load on the respiratory muscles is increased in COPD (Jolley & Moxham 2009) the sensation of respiratory effort and therefore of breathlessness is also increased. This study aimed to assess if the 6-minute protocol described earlier (Section 3.6) could differentiate between COPD patients and healthy individuals.

7.4.2 Method

Participants
Nineteen individuals (9F:10M; age range 44-75yrs) with clinical diagnosis of COPD (FEV₁ % pred 44 ± 13; FEV₁/FVC ratio 54 ± 14) were asked to undertake two 6-minute seated R_{k} trials (Section 3.1.3.2). Upon gaining consent, body weight and height were measured and baseline spirometry performed (Section 3.4.1).

Protocol
A standard 6-minute seated R_{k} protocol was followed (Section 4.6) and the R_{k} load was set at 0 and 0.75 kPa.L.sec⁻¹.

Data Analysis
At the end of the test the following study parameters for each breath were calculated; V_{T_{1}} (ml), V_{T_{1}}\Delta \text{L} (L.sec⁻¹) and InW_{m}mouth (J.L) (Section 3.1.6). t-test’s were used to assess for significance difference between R_{k} loads and with control data described earlier (Section 4.2).

7.4.3 Results
COPD patients had a higher f_{r} than controls in both trials, although for both groups it remained constant irrespective of R_{k} load. V_{T_{1}} remained constant irrespective of participant group or applied R_{k} load. The increase in InW_{m}mouth observed previously in control subjects when an R_{k} load of 0.75 kPa.L.sec⁻¹ was applied was observed in the COPD patients. This increase was similar in magnitude to that observed in control subjects approximately doubling from trials at 0 kPa.L.sec⁻¹.
While the change in InWrs\textsuperscript{mouth} was similar in COPD patients and controls, it was observed to be significantly higher in COPD as opposed to control subjects at both levels of R\textsubscript{K} (0 and 0.75 kPa.L.sec\textsuperscript{-1}) (Fig 7.4).

### 7.4.4 Discussion
A 6-minute trial using an applied R\textsubscript{K} load is able to differentiate between COPD patients and healthy individuals as assessed by InWrs\textsuperscript{mouth}. When completing a 6-minute protocol as outlined in Section 4.6, COPD patients had a InWrs\textsuperscript{mouth} of -0.40 ± 0.15 (J.L), 20% greater than that reported for healthy controls (Section 4.6).

Although COPD patients had a higher f\textsubscript{R} this remained constant in both trials alongside the constant ventilation rate would suggest that the increased inspiratory work (InWrs\textsuperscript{mouth}) is a result of COPD. The hyperinflation of COPD reduces the flow and pressure generating capacity of the diaphragm (Mckenzie et al 2009). The ratio of t\textsubscript{i} to t\textsubscript{Tot} is reduced in COPD in an effort to increase the time for available for expiration and minimise hyperinflation which demands an increase inspiratory flow rate (Jolley & Moxham 2009).
Figure 7.4: (A) $f_R$ (bpm$^{-1}$) (B) $VT_1$ (L) and (C) InWrs$^{mouth}$ (J.L) in Healthy Controls (Black bars) COPD patients (Grey Bars) During 6-minute Trials With $R_K$ at 0 and 0.75 kPa.L.sec$^{-1}$. * = sig diff ($p<0.05$) with trial at 0 kPa.L.sec$^{-1}$.
7.5 COPD TBPA

7.5.1 Introduction

The inspiratory and expiratory airflow profile differs in the presence of airway obstruction and an analysis of the inspiratory and expiratory airflow profile has shown there to be quantifiable changes in the airflow profile in the presence of airway obstruction (Colsanti et al 2004). In COPD the severity of the disease is related to the degree of airway obstruction with the spirometric measurement of FEV$_1$ providing the gold standard method for assessing the degree of airway obstruction. As discussed previously there are occasions when it is not always possible to accurately perform FEV$_1$ measurement in COPD. The more severe COPD becomes the more difficult it can be to measure lung function as patients get older, suffer from comorbidities and frequent exacerbations. Even if patients fully co-operate, current lung function guidelines often label measurements as low quality and not good enough for assessment, meaning the patients most at risk are the hardest to assess (Soriano & Miravitllies 2009).

The aim of this study was to assess the tidal airflow profile analysis equations developed by Colsanti et al 2004 (Section 3.2.1), as an alternate measure of airway obstruction, as FEV$_{1\text{TAP}}$, in COPD patients and compare this with data previously reported for healthy controls (Section 5.4).

7.5.2 Method

Thirty-one patients (Age range 44-84: 18M:13F) with a clinical definition of COPD (FEV$_1$ % pred; 44 ± 15) were asked, whilst seated and relaxed, to breathe through a pneumotachograph for three minutes to measure TBPA (described in Section 3.2). Spirometry provided the measured FEV$_1$ (Section 3.4) while FEV$_{1\text{TAP}}$ was derived using the equation described previously (Section 3.2): COPD FEV$_{1\text{TAP}}$ = -3.73 + (t$_{PPEF80}$ x 0.031) + (t$_{PTIF}$ x 6.08) + (Age x -0.017). Linear regression was used to assess for relationship between FEV$_1$ and FEV$_{1\text{TAP}}$, and the difference between FEV$_1$ and FEV$_{1\text{TAP}}$ was also calculated.

7.5.3 Results

The three minutes of resting breathing was well tolerated by all COPD patients and all trials were completed successfully. The average resting f$_R$ was found to be 17±4 bpm$^{-1}$. The relationship between FEV$_{1\text{TAP}}$ and measured FEV$_1$ was $r^2$ 0.38 p <0.01, (Fig 7.5) which is less than that reported for healthy controls ($r^2$ 0.57 p<0.001 Section 5.4). FEV$_{1\text{TAP}}$ was seen to under-predict FEV$_1$ in COPD by -0.154ml and over-predict in controls by 0.123ml (Figure 7.6).
7.5.4 Discussion

Simple tidal breathing profile analysis provides a useful method for assessing airway obstruction in both controls and COPD patients. The appropriate TAP analysis provides a
quantitative measure of airway obstruction that can be used to provide a surrogate measure of FEV$_1$. The data suggests that refinement of the predictive equations of Colsanti et al 2004 needs to be conducted to produce a more linear model.

7.6 Summary & Conclusion

In Summary……

In this chapter I set up and ran 3 clinical trials recruiting 50 COPD patients who undertook 38 R$_K$ trials and 31 TBPA trials.

The Participant

- COPD patients are keen to take part and get involved with research into their condition.
- Many of these find completing maximal spirometry manoeuvres difficult.

The Test

- COPD patients were able to successfully undertake R$_K$ and TBPA trials.
- The R$_K$ protocol described previously is able to detect differences between individuals with chest disease and healthy controls.
- TBPA can be used to predict FEV$_1$ although more work is needed to develop the accuracy of the equations developed by Colsanti et al.
- The hypothesis set out in section 7.0 is confirmed

COPD is a widespread and common disease affecting many individuals and providing a significant burden to healthcare provision in the UK and is a particular health problem in Rhonda Cynon Taf where the patients recruited for the studies described reside. In the engagement activities described these patients were keen to take part and get involved with relevant research taking place locally. As such the current studies and links made with local patients and healthcare professionals involved with respiratory disease provides a strong base for future research work into COPD.

COPD is a treatable disease, the symptoms of which can be actively managed to improve the symptoms and quality of life patients. These patients should not be ‘written off’, the patients I met were keen, motivated and interested and represent a valuable resource to those involved in research into COPD. The physiological impact of daily activities that cause breathlessness in COPD should also be considered in terms of their impact on the load and capacity of the
respiratory muscles and the neuro-mechanical disassociation that results (Jolley & Moxham 2009).

Within the wider literature there is a paucity of work on non-invasive techniques of assessing respiratory endurance or the work of breathing (WOB) with studies usually relying on established invasive methods using internal balloon catheters to assess WOB (Section 1.11) even in studies of non-invasive ventilation (Girault et al 2009). Using an invasive method Delwegg et al (2008) reports large differences in WOB between healthy controls and COPD patients although in their methodology they report the use of default values for chest wall compliance and it is unclear if this is the reason for the magnitude of the differences observed. Furthermore they use a range of set f_R (from ~7 to 30 bpm^{-1}) however the sample length was not changed (40 breaths). Therefore a trial with a f_R of ~30 bpm^{-1} would be completed in just over a minute, while a trial at ~7 bpm^{-1}, would take almost 6 minutes which makes it difficult to assess whether a participant is in steady state workload or is liable to fatigue but prevented from doing so by the short sample length.

The R_K protocol was able to differentiate between healthy individuals and those with COPD, however the healthy controls assessed in Chapter 4 were not age matched to the patients described in this chapter. While it is not clear if lnWrs_{mouth} is affected by the same age related decline as that seen in FEV_1 (Section 7.1), if suitable healthy aged matched controls could be recruited it would allow the impact of COPD on lnWrs_{mouth} to be studied irrespective of age. While Delwegg et al (2008) found differences in the WOB they also failed to age match healthy controls with COPD study group which would suggest this further work would be a useful undertaking.

Exercise was seen to affect lnWrs_{mouth} in healthy controls and this suggests that it would also have an affect on COPD patients. While these younger subjects exercised at relatively higher exercise intensities, with 6-minute walking tests routinely used in COPD assessment there appear no obvious contra-indications for COPD patients to complete R_K trials whilst completing such sub-maximal exercise. Calculating lnWrs_{mouth} could provide additionally useful information about a patient’s respiratory endurance capability alongside their exercise endurance.
While TBPA was able to estimate FEV₁ the data suggests that further refinement of the predictive equations is required to improve this estimation. Furthermore the use of two equations complicates the practical use of TBPA, in that an existing diagnosis of respiratory health is required to select the correct equation. By combing all data future work should be focused on developing a single predictive equation that can be applied irrespective of respiratory status.

Both of the techniques (Rₖ trial and TBPA) assessed in this chapter represent sub-maximal methods of 1) differentiating between disease and 2) estimating FEV₁. While neither represent a finalised approach they provide a basis for future research into sub-maximal testing within this patients group.
Chapter 8 – Lung function in preterm and term children

8.0 Introduction and Overview
The work detailed in this chapter took place as part of a collaborative study with Prof. Sailesh Kotecha and Dr Suchita Yoshi of the Department of Child Health at Cardiff University. This Cardiac and Respiratory Outcomes of Prematurity (CROP) study was led by Prof Kotecha, while Dr Yoshi was responsible for recruiting the participants. However the work described in this chapter was undertaken by the thesis author.

The primary aim of this study was to assess the differences between children born extremely pre term (less than 32 weeks) with and without bronco-pulmonary dysplasia, also referred to as Chronic Lung Disease (CLD) of prematurity and with children born at full term (≥38 weeks). The assessment of InWrs\textsuperscript{mouth} and TBPA in these children is then outlined and the relationship with exercise and activity levels explored. The hypothesis that chapter seeks to test is that R\textsubscript{K} trials can differentiate between children born preterm, preterm with CLD and at full term.

8.1 Background to Chronic Lung Disease in Prematurity
Current neonatal intensive care has greatly improved the survival of preterm infants and mechanical ventilation and oxygen therapy is the mainstay of pulmonary care in premature infants. However despite advances in neonatal intensive care, many preterm infants remain oxygen dependent beyond 36 weeks of corrected gestational age and they develop CLD. In recent years, with the widespread use of antenatal steroids, postnatal surfactant and less aggressive mechanical ventilation, the pathophysiology of CLD has changed. However, the number of children with CLD is ever increasing.

Infants who die from CLD are shown to have markedly decreased numbers of alveoli and their medium sized airways and their pulmonary arteries have a thicker smooth muscle layer
(Margraf et al 1991), which can result in chronic obstructive airway disease and pulmonary arterial hypertension respectively (Abman et al 1985, 2002, Benatar et al 1995). Among those who survive, whilst the majority of the infants with CLD can be weaned off oxygen by 2 years of age, the question arises whether these pathological changes at an early age contribute to diminished lung function and increased pulmonary vascular resistance later in life, especially, in response to hypoxia.

Limited information is available about the long term cardio-respiratory function in school aged children born prematurely, especially, in more recent populations who have been treated with surfactant. Term and near term infants who had persistent pulmonary hypertension of the newborn during infancy when studied at 20 years of age at sea level and at high altitude, were noted to have significantly greater increases in their pulmonary arterial pressures, at high altitude, compared to normal controls (Sartori et al 1999). Follow up of lung function and exercise capacity in young adults born prematurely, has shown that at a mean age of 19 years lung function parameters were within normal ranges, but compared to control subjects, they had evidence of airway obstruction, lower CO diffusing capacity and lower exercise tolerance (Vrijlandt et al 2006). However, this data pre-dates the use of surfactant and modern ventilation techniques.

Although survival of preterm infants has improved there is limited data on longer term outcomes in these children. As these children may be at risk of developing COPD and pulmonary hypertension in later life, especially if they smoke, it is clearly important to assess the longer term risks of surviving CLD of prematurity.

This chapter investigates if these children, on reaching 8-12 years of age still have persisting sub-clinical abnormalities which may have longer term implications on their health.

8.2 Work of Breathing and Exercise in Preterm and Term Children

8.2.1 Method
Seventy-five children (37M:38F: age range 8-12) who fulfilled inclusion (Fig 8.1) and exclusion criteria (Fig 8.2) were recruited into either study group 1, 2 or 3 (Fig 8.1). Preterm infants (<32 weeks of gestational age) who were born or cared for in the Special Care Baby Unit at the University Hospital of Wales (UHW), Cardiff from 1995 to 1999 were identified from the Neonatal Database maintained at UHW. A suitable cohort of healthy term children of similar age and gender matched control group were also recruited.
Group 1: Preterm with CLD Children who were born prematurely at $\leq 32$ weeks of gestational age and who had oxygen dependency beyond 36 weeks of corrected gestational age.

Group 2: Preterm without CLD Children who were born prematurely at $\leq 32$ weeks of gestational age but did not have oxygen dependency beyond 36 weeks of corrected gestational age.

Group 3: Term Control Age and gender matched healthy control children born at full term (38 complete weeks or more).

Figure 8.1: Group Inclusion Criteria

- Children with significant congenital structural cardiac defect
- Children with significant congenital structural respiratory tract defect
- Children with significant persisting cardio-respiratory abnormalities requiring therapy, including oxygen therapy
- Children with any neuromuscular disease that could compromise cardiac or lung function
- Children with severe neuro-developmental impairment who would not be able to comply with the research procedures

Figure 8.2: Study Exclusion Criteria

Protocol
After children gave their assent and informed consent was obtained from their parents or guardians, each child’s height and weight was recorded. Children were initially coached using a spriometer with a specially designed programme incorporating graphics to explain how an FEV$_1$ manoeuvre should be properly conducted. The child was given as many practice attempts as necessary to achieve a suitable test result. After a short period baseline spirometry was then performed (Section 3.4.1). A standard 6 minute work of breathing protocol (Section 4.6) was undertaken with the $R_k$ load set at 0.75 kPa.L.sec.$^{-1}$. A bespoke metronome (Section 3.3) was used to maintain $f_R$ at 18 bpm$^{-1}$. At the end of each trial the following study parameters were calculated per breath; $V_T$ (ml), $V_T/t_{i}$ (L.sec$^{-1}$) and $InWr_{mouth}$ (J.L) (Section 3.1.6).
To assess \( \dot{V}O_2 \) max an incremental cycle ergometer protocol was followed (Section 3.5.1) with the load being increased by 30 watts every 3 minutes at a cadence of \( \sim 65 \) rpm until the child indicated they could not continue or they could not maintain pedal cadence. The following parameters were measured; \( \dot{V}O_2 \), \( \dot{V}CO_2 \), \( \dot{V}E \) and \( f_R \) using an online gas analysis system (Viasys Masterscreen: MS-CPX) allowing the respiratory exchange ratio (RER) to be calculated; \( f_H^{-1} \) using a heart rate belt (Polar Ltd, UK); and rate of perceived exertion (RPE) using a Borg scale (Borg 1982). To attain \( \dot{V}O_2 \) max children had to exercise to at least 80% of their age predicted \( f_H \) maximum, and/or an RER > 1.0.

**Safety**

During this study, if any prematurely born child was noted to have abnormal test results compared to the control children, it was arranged for these children to be followed up by Paediatric Cardiology and Respiratory Consultants at UHW, who were part of the research team associated with the study.

**Data Analysis**

A one way ANOVA was used to assess for significant difference between the three groups.

### 8.2.2 Results

All children successfully completed baseline spirometry. Sixty-three children successfully completed the \( \dot{V}O_2 \) max protocol, three trials were lost to technical failure, two because the children were too short for the ergometer and six because they did not achieve maximal criteria. Sixty children completed the \( \dot{R}_K \) trial, fifteen were excluded as they were not able to follow instruction. Fifty-four children were able to complete all three tests with the failure rate evenly distributed between the three groups (Table 8.1). Data for all subjects is shown in Table 8.2.

In the children who completed all tests, when \( \dot{V}_E \) from the work of breathing trial was compared to the maximal \( \dot{V}_E \) from the \( \dot{V}O_2 \) max trial, a ratio could be calculated that indicated how resting \( \dot{V}_E \) could be increased during maximal exercise. In those children with a \( \dot{V}_E \) ratio of < 3.5 they had a significantly lower \( \dot{V}O_2 \) max (30.3 ± 8.5 versus 35.4 ± 7.2, ml.kg.min\(^{-1}\); \( p<0.05 \)) and a higher InWrs\(^{mouth}\) (0.47 ± 0.11 versus 0.29 ± 0.05 J.L\(^{-1}\); \( p<0.001 \)) but no differences in FEV\(_1\)%pred. As this ratio dropped below 3.5, InWrs\(^{mouth}\) was seen to rise exponentially, \( r^2 = 0.6 \) (Fig 8.3). Of the seven subjects who were identified with a
$\dot{V}_e$ ratio $< 3.5$ and $\text{InWrs}^{\text{mouth}} > -0.45$ there were no significant differences in any FEV$_1$%pred suggesting that there may be another factor such as increased airway resistance that might be a causative factor.

**Table 8.1: Number of Children Completing Study Trials; Successful (Unsuccessful)**

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>n = Successful</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$%pred</td>
<td>23 (0)</td>
<td>25 (0)</td>
<td>27 (0)</td>
<td>75</td>
</tr>
<tr>
<td>VO$_2$ max</td>
<td>19(4)</td>
<td>20(5)</td>
<td>24(3)</td>
<td>63</td>
</tr>
<tr>
<td>(ml.kg.min$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>InWrs$^{\text{mouth}}$ (J.L)</td>
<td>18(5)</td>
<td>20(5)</td>
<td>22(5)</td>
<td>60</td>
</tr>
<tr>
<td><strong>All tests</strong></td>
<td>17(6)</td>
<td>18(07)</td>
<td>19(7)</td>
<td>54</td>
</tr>
</tbody>
</table>

**Table 8.2: Outcomes in Three Groups**

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Height (cm)</strong></td>
<td>140 ± 9</td>
<td>143 ± 9</td>
<td>143 ± 11</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>33 ± 8</td>
<td>40 ± 12</td>
<td>41 ± 14</td>
<td>ns</td>
</tr>
<tr>
<td>FEV$_1$%pred</td>
<td>81 ± 14</td>
<td>92 ± 15</td>
<td>98 ± 12</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>InWrs$^{\text{mouth}}$ (J.L)</td>
<td>-0.33 ± 0.1</td>
<td>-0.37 ± 0.1</td>
<td>-0.30 ± 0.1</td>
<td>ns</td>
</tr>
<tr>
<td>VO$_2$ max (ml.kg.min$^{-1}$)</td>
<td>35.9 ± 6.2</td>
<td>36.1 ± 7.6</td>
<td>30.6 ± 8.4</td>
<td>ns</td>
</tr>
</tbody>
</table>
Figure 8.3: Relationship of $\frac{\dot{V}_E}{V}$ Ratio and InWrs$^{\text{mouth}}$
8.3 TBPA in Preterm and Term Children

Due to the inherent problems involved with assessing the respiratory status of children discussed previously, a technique that would reduce the level of active participation required would be a useful alternative to standard tests. The previous work of Colsanti and colleagues only developed predictive equations for FEV$_{1\text{TAP}}$ in children with CF. This section details the development of predictive equations of FEV$_{1\text{TAP}}$ using raw airflow data gathered from the children tasking part in the CROP study.

8.3.1 Method

The seventy five children described previously (Section 8.2) undertook a three minute TBPA trial as described in Section 3.2. The children were assessed independently of their CROP study group status previously described (Fig 8.1) and were classified as either having a FEV$_1$%pred of <80% or ≥ 80%. Using a statistical software package (Sigma Plot version 9) stepwise linear regression analysis was used to develop predictive equations of FEV$_{1\text{TAP}}$. Key factors integrated into the analysis were height and $t_{\text{TPEF80}}$.

8.3.2 Results

Seventy-five children successfully completed the TBPA protocol, Data for 5 children was lost due to technical problems with 1 child unable to follow trial instructions. Characteristics of the children who successfully completed the trial can be seen in Table 8.3. For both groups as would be expected height was a strong predictor of FEV$_1$. However in both groups when $t_{\text{TPEF80}}$ was integrated into the regression analysis the fit ($r^2$) was better than if height was used alone (<80% 0.74 vs 0.69: ≥ 80% 0.75 vs 0.60). The regression equations for each group are plotted in Fig 8.4.

<table>
<thead>
<tr>
<th>Table 8.3: Characteristics of Sixty-Nine Children Who Completed TBPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>FEV$_1$%pred &lt;80%</td>
</tr>
<tr>
<td>FEV$_1$%pred ≥ 80%</td>
</tr>
</tbody>
</table>
Figure 8.4: FEV$_{1\text{TAP}}$ predictive equations of children in CROP study. FEV$_1\%p < 80\%$: \( \text{FEV}_{1\text{TAP}} = -5.830 + (0.0361 \times \text{Height(cm)}) + (0.0143 \times t_{\text{PTEF80}}) \). FEV$_1\%p \geq 80\%$: \( \text{FEV}_{1\text{TAP}} = -2.951 + (0.0372 \times \text{Height(cm)}) - (0.00215 \times t_{\text{PTEF80}}) \).
8.4 Summary and Conclusions

**In Summary……..**

In this chapter 75 children undertook Rk, TBPA and VO\(_2\) max trials as part of a wider study into the effects of prematurity on cardio-respiratory development.

*The Participant*

- Children often required substantial coaching to complete the tests required of them, although the amount of time spent with each individual child was not recorded.
- Despite a relatively intensive testing protocol the majority children were able to complete these trials.

*The Test*

- The only outcome that was significantly different between the three study groups was in FEV\(_1\)% pred.
- Spirometry was successfully completed by all although this was most probably due to level of training provided.
- Data indicates an exponential relationship between InWrs\(_{\text{mouth}}\) and the ability to increase ventilation during maximal exercise that was independent of gestational status.
- Using raw air flow data a predictive TBPA equation was developed for future use.
- In the context of Rk trials the hypothesis set out in section 8.0 is rejected.

While a significant difference in FEV\(_1\) was identified between the three study groups there was considerable overlap in terms of other outcomes which may suggest that the arbitrary definition of CLD is too simplistic to be used as means of differentiation with other preterm children. There may be other factors such as a reduction in diffusion capacity, increased airway resistance or lung hyperinflation that may have resulted from their premature status that could be used instead as more objective measures for classification.

Within the cohort VO\(_2\) max appear to be independent of study group status. This is most likely due to how the cardiovascular system develops much earlier in-utero than the respiratory system so a lack of difference is to be expected. Perhaps a more pertinent questions is how (if at all) does an impaired respiratory system (as reduced FEV\(_1\)) impact on
the cardiovascular system? While the majority of children appeared symptomatically well and active further study of this cohort would provide useful information about how children born prematurely develop as they grow. For example, do the differences in FEV$_1$ exist into adulthood? Could there be a link between gestational age and the impact of respiratory disease in later life? Should such children be specifically targeted to prevent behaviours that may adversely impact on their respiratory health such as tobacco smoking and environmental exposures?

A valid goal of future assessment of respiratory function in children would be to develop techniques that provide less instruction while maintaining an adequate level of diagnosis. The development of a predictive TBPA equation would allow this to occur and provides a basis for future work in a similar manner to that undertaken in COPD patients (Section 7.5). However the relatively small group numbers prevent a robust equation from being developed and much larger cohort would be required but with the relatively successful testing and simple protocol this could be relatively easy to undertake.
Chapter 9 – Resistive load detection

9.0 Introduction & Overview

Breathlessness is a common reason for referral for lung function assessment (Jefferies & Turley 1999). Breathlessness or dyspnoea is a subjective difficulty, or distress in breathing and it can therefore be difficult to accurately quantify. Breathlessness can be closely linked to chest diseases in which airway obstruction is a common characteristic. This can be permanent obstruction such as with COPD or recurrent reversible airway obstruction caused by airway hyper-responsiveness such as with asthma. Accurate perception of changes in airway obstruction is a critical component in the self-management of chest disease (McQuaid et al 1996).

In healthy subjects quantification of the changes in mechanical load is a relatively simple task but this may be more difficult in diseases with airway obstruction. Typically 15-40% of adults with asthma fail to consistently recognise clinically significant breathing changes and better perceptual accuracy is associated with significantly less functional morbidity (Fritz et al 1999). Failure to perceive symptoms of an oncoming asthma ‘attack’ has been suggested as one of the reasons for a delay in patients seeking treatments which can then lead to life-threatening events (Davenport & Kifle 2001).

Existing methods for quantifying dyspnoea use mechanical loads that are related directly to airflow (Wiley & Zechman 1966; McQuaid et al 1996; Davenport & Kifle 2001). This chapter outlines the development and use of a new technique, using a computer driven device where a resistive load ($R_K$) can be maintained irrespective of the airflow rate. The aim of this chapter is to quantify the ability to detect $R_K$’s load in healthy controls and patients with obstructive disease. The hypothesis that chapter seeks to test is that a resistive detection method using $R_K$ loads can differentiate between COPD patients and healthy individuals.
In addition the possible protocol format for a resistive detection trial was studied. Previous studies apply resistive loads in a random fashion, however physiological detection tests in other areas of human physiology use protocols that apply loads in descending order, for example audiometry. The British Society of Audiology (2004) outlines a trial that uses descending levels for detection. This raises the question; Is there any difference between random and descending protocols on perceptual ability?

9.1 Method; Healthy Control

Participants

Eleven healthy males (age range 18-29yrs; FEV$_1$%pred 99±14) after completing static and dynamic lung function measurements (Section 3.41 and 3.42), undertook a series of resistive load detection trials on two separate visits. For all trials each subject breathed through the experimental set up (Fig 9.1) via a mouthpiece and bacterial filter. All subjects wore nose clips and had no prior experience of the device. Written informed consent was secured before testing took place.

Experimental set up

The $R_k$ device was combined in series with an analogue digital converter (ADi Powerlab ADinstruments) which included a pneumotachograph and push button device with a small rubber gasket to endure an air tight seal (Fig 9.1).

Figure 9.1: Experimental Set-up
The $R_K$ device was used to apply an $R_K$ load during quiet tidal breathing and if a participant detected a resistive load they were instructed to push the button. Using commercially available software (Chart5, ADinstruments) this response could be recorded concurrently with the flow signal from the pneumotachograph and an electronic mark of the loaded phases to provide a record of each trial (Fig 9.2).

![Figure 9.2: Recording of resistive detection trial using Chart5 software.](image)

**Figure 9.2: Recording of resistive detection trial using Chart5 software.** (A) Participant response to $R_K$ load; (B) Air Flow; and (C) Digital Marker of onset of applied $R_K$ load.

**Development of Protocol - Loaded phase cycle**

In a similar manner to Wiley & Zechman (1966), $R_K$ loads were applied in two breath cycles, as they describe that this can be used to avoid possible chemical influences in the detection resulting from blood gas changes, produced by possible reductions in alveolar ventilation that could occur over larger period of breathing cycles. For example an earlier study by Bennet et al (1962) employed a five breath loaded cycle. Subsequent studies have used a similar two breath loaded cycle (Puddy et al. 1992; McQuaid et al. 1996; Fritz et al. 1999), however Davenport & Kifle (2001) used a single breath loaded cycle.

**Number of loads applied during how many trials?**

Wiley & Zechman (1966) used eight individual loads applied once over a maximum of three trials McQuaid et al (1996) and Fritz et al (1999) used five individual loads applied twenty-five times during one trial. Davenport & Kifle (2001) used one trial of nine individual loads applied four times, and two trials of nine loads applied three times. For this study it was
planned to compare two protocols (descending and random) and that each was to be repeated twice. Therefore each load was applied once in four trials which was similar to that described in these previous studies and would not be unduly taxing on study participants.

**Level of applied load**

As the $R_K$ device described in this thesis was to be used, the $R_K$ loads that were studied previously (Chapter 4) were used in this study: $0.15 – 1.5 \text{ kPa.L.sec}^{-1} (1.5 – 15.3\text{cmH}_2\text{O})$.

**Instruction to participants**

Participants were given a demonstration trial of two breaths loaded at the highest $R_K$ that they would experience in the subsequent trials. They were told when the load was applied and were instructed to simultaneously depress the push button. Previously studies used a push button for participants to indicate they had detected loads however not all followed the same instruction protocol. Davenport et al (2001) had participants listen to music to mask any experimental sounds, Puddy et al (1992); McQuaid et al (1996) and Fritz et al (1999) informed participants with a signal light that a resistance was about to be applied. Wiley et al (1966) describes how the operator “stood behind a curtain and manipulated the apparatus quietly” so to give no indication to the subject when loads were applied.

An issue with the $R_K$ device is that as it continually changes its internal diameter to maintain a constant $R_K$, it produces an audible noise. Therefore in the unloaded phases the device was set at an $R_K$ of $0.01 \text{ kPa.L.sec}^{-1}$ so that the device would continue to make an operating sound and the lack or onset of any noise could not be used as an indication of a loaded breath.

**Visit 1**

Protocol A – Participants followed a protocol with $R_K$ descending loads from $1.5, 1.25, 1.0, 0.75, 0.5, 0.3, 0.2$ to $0.15 \text{ kPa.L.sec}^{-1}$. This is similar to the British Audiological Society’s guidelines that apply hearing tests in a descending fashion.

**Protocol B** – The same eight $R_K$ loads as in protocol A were applied in a random order which was selected from a prepared random list for each participants so that all followed a different order.

Participants undertook both protocols twice completing four trials in all on their first visit.
Unloaded breaths between loaded phases varied from 3 – 8 breaths in a preset, non-systematic order to prevent temporal sequence detection. This order was used for all participants to allow for comparison. These periods used between loaded phases are shorter than that described by Wiley & Zechman (1966); (4-20 unloaded breaths), but similar to those reported by Davenport & Kifle (2001); (3-6 unloaded breaths) and Puddy et al (1992); (5-10 unloaded breaths). Fritz et al (1999) used 3 unloaded breaths between each loaded phase.

Protocol - Visit 2
In a similar manner to their first visit, participants undertook four trials each with eight R_K loaded phases. On this visit however each trial had eight identical loads at 1.0, 0.75, 0.5 and 0.25 kPa.L.sec⁻¹ so that the repeatability of detection of each level could be ascertained.

Data Analysis
For assessing detection a similar method was used to that described by Wiley & Zechman (1996), the percent detection for trials was calculated by dividing the number of successful detections by the maximum possible and multiplying by 100.

9.1.1 Method: Obstructive patients
A group of patients (n=5; median MRC Dyspnoea score 4) with clinically diagnosed asthma (n=2F: age range 40-51; FEV₁%pred 84-102; MRC) and COPD (n=3(2M) age range 60-65; FEV₁%pred 25-49) were invited to undertake a breathless sensitivity trial. These patients followed protocol A in a similar fashion to that outlined in Section 9.1.2, however due to time constraints these patients were only asked to complete the protocol once.

9.2 Results
All controls and patients were able to complete all sensitivity trials and none were halted early. During constant protocol trials when R_K was at 1 kPa.L.sec⁻¹ percentage detection rate in healthy controls was 99% falling to 8% at an R_K load of 0.25kPa.L.sec⁻¹ (Fig 9.3). A percentage detection rate of 50% would appear to occur at R_K load of approximately 0.55 kPa.L.sec⁻¹. The rate of decline in percentage was similar in Protocol A and B although the decline was steeper in protocol B between R_K loads of 0.3 and 0.75 (Figure 9.4). Chest disease patients displayed similar detection rates above 0.75 kPa.L.sec⁻¹ but this dropped to zero detection below this R_K load (Fig 9.5).
Figure 9.3: Percent detection in healthy controls (Mean ± SEM) of $R_K$ constant protocol during 2nd visit.

Figure 9.4: Percent detection in healthy controls (Mean ± SEM) of $R_K$ during protocol A & B
Figure 9.5: Percentage detection in chest disease patients (Mean ± SEM) of $R_k$ during protocol A
9.3 Summary and Conclusion

In Summary……..

In this chapter a novel system to detect sensitivity to resistive loads was developed. Using this 11 control subjects and 5 patients undertook 85 breathless sensitivity trials.

1. The Participant
   - All participants were able to complete all sensitivity trials with relatively little training.
   - Substantial mental cooperation was required in terms of concentration but the trials themselves required comparatively little physical effort.

2. The Test
   - Repeatability of detection of resistive loads was good (>90%) in healthy controls when the $R_K$ Load was over 0.75 kPa.L.sec$^{-1}$ however it dropped when $R_K$ load was below 0.5kPa.L.sec$^{-1}$.
   - Healthy controls showed a graded decline in protocols A and B, although this decline was slower in protocol A where the resistances were applied in a sequential order suggesting that this may have caused the better detection rates.
   - Data would suggest that patients with chest disease are unable to detect $R_K$ loads below 0.75kPa.L.sec$^{-1}$.
   - Although testing only took place in a limited number of COPD patients, data suggests that this technique could be used to differentiate between health and disease confirming the experimental hypothesis set out in section 9.0.

This chapter describes the development of a novel system to assess the ability to detect resistive loads. This system has benefits over existing methods (described in Section 9.1) such as; easily integrating an applied load and the response by a participant; allowing the level and duration of the resistive load to be easily adapted in a manner that avoids alerting the trial participant; and using a resistive load that is independent of airflow.

In healthy controls both protocol A and B showed a similar decline in detection rates as $R_K$ load decreased. This would suggest that this method could be used to evaluate the level of sensitivity in these individuals. Furthermore comparison between individuals who are able to detect $R_K$ loads below 0.5 versus those unable could be conducted. However this would
require further lung function testing that was unfortunately not conducted for this study, specifically markers of airway obstruction such as $R_{AW}$.

Interestingly the decline in the mid-range of $R_K$ loads were seen to be less steep in protocol A than B. In short when the $R_K$ was decreased sequentially the detection rate was better than when the $R_K$ loads were applied in a random order, suggesting that participants were using the order to assist with the detection of $R_K$ loads at this point (Fig 9.4). This temporal patterning questions the utility of sequentially descending protocols in other physiological tests such as those used by the British Audiological Society. Do they overestimate these audiological test scores?

The testing of patients was undertaken concurrently with the testing of the healthy controls in an ad-hoc fashion while studies for other chapters in this thesis took place. It would be useful to repeat the methodology undertaken by the controls to elicit what similar levels of repeatability exist. Although conducted in only limited trials the patient data indicates that there is limit to detection of $R_K$ loads below 0.75 kPa.L.sec$^{-1}$ in patients with clinically diagnosed asthma and COPD. It is however unclear where the exact point may be and future work would benefit from looking at more loads between the points identified in this chapter (0.5 – 1.0 kPa.L.sec$^{-1}$). These patients had a high median MRC Dyspnoea score of 4 which could suggest that the breathlessness detection protocol described could be used to quantify breathlessness.

The methodologies of previous studies were used to inform the development of the protocol that was used in this study. However where this significantly differs is in the magnitude of the resistive loads applied. Wiley & Zechman (1966) applied eight loads between 0.2 - 1.8 cmH$_2$O (0.02-0.18kPa), Fritz et al (1999) applied loads ranging from 0.25 – 8 cmH$_2$O (0.02-0.78 kPa), whereas McQuaid et al (1996) applied a percentage (20, 60, 100, 140, 180%) of subjects baseline $R_{EFF}$. The early work in this thesis suggested that when using the $R_K$ device in this way, greater loads would be needed for example between 0.25 – 1.5 kPa.L.sec$^{-1}$. The graded responses as $R_K$ decreased seen in Figures 9.2, 9.3, and 9.4 shows this to be the case. It is unclear why such there is such a magnitude of difference with these previous studies, but is most probably due to the flow dependent loads used.
Chapter 10 – Thesis Summary

Assessment of respiratory function can be difficult to accurately complete due to the complex interaction of different human biological systems and the reliance on the willingness and cooperation of the individual being assessed. Techniques have been developed that are accurate, reliable and repeatable, yet they frequently come with some caveat that affects their utility. These can include requiring maximal participant effort and in some circumstances involve invasive measurement techniques. Where possible the use of such approaches is the best method however, this is not always achievable. What should not be inferred is that maximal and/or invasive tests are somehow inferior to non-invasive tests. As was stated in the beginning of this thesis (Section 1.0) the aim of developing new methods of assessing the respiratory system was not to replace or supersede these established methods but to provide new approaches when their use was not possible. For example the gold standard measurement of the respiratory system that is most commonly used as a marker of respiratory health is spirometry (Section 1.5.1), although situations occur when it may not be possible to use such a technique, such as with young children, exacerbating patients or when a lack of equipment and/or trained staff is available (Section 1.6).

The work in this thesis also details how meaningful these new techniques (TBPA and \( R_K \) trials) are, as their efficacy is directly related to their ability to reliably and repeatable act as measures of the respiratory system. The experimental work in chapters 6 to 9 was driven by the expectation that these new approaches would be able to differentiate between rest and exercise, and health and disease. The meaningfulness of these techniques to provide useful measures would then be represented by this ability. This approach was taken due, in particular to \( R_K \) trials and the difficulties identified with the definition and measurement of endurance (Chapter 2), and the lack of any recognised measure with which to compare them with (Section 2.2.13). To derive the absolute physiological mechanisms underpinning of each technique was not the goal of this thesis, rather their practical ability to be used safely and easily, and their use in differentiating between rest and exercise, health and disease.

The focus of this thesis has been to develop sub-maximal tests that reduce the need for active participation allowing a passive participation, which will also simplify testing by reducing the need for complex equipment and trained staff.

The main aims of this thesis were to investigate this sub-maximal focus using two alternative
methods: Respiratory Muscle Endurance; and expiratory tidal profile analysis and it investigated these in detail. Additionally it was identified that any new methods should be viewed from two points to assess the validity of any outcomes: 1) The Test – how well did these new methods represent respiratory function; and 2) The Participant – how well did participants interact with these new methods.

The work describes how 99 adult participants (68 Healthy controls and 31 COPD patients) and 75 children (48 clinical group and 27 healthy controls) were recruited and completed 467 respiratory endurance trials whilst seated and exercising, and 249 relaxed tidal breathing trials.

10.1 The Test
From a systematic review of 111 journal articles it was identified that the terms endurance and fatigue are both frequently used on the (incorrect) assumption that they are interchangeable. This lack of clarity and confusion has resulted in no clear definition or protocol to assess respiratory muscle endurance. Attention should also be drawn to the use of ‘muscle’ in these terms. Non-invasive tests cannot differentiate between different components of the respiratory system and as such they cannot measure the respiratory muscles per se. Respiratory endurance or respiratory system endurance would be a more suitable term.

With regards to a more accurate definition of endurance it was argued that as it represents the property that affords resistance to fatigue, for example when endurance fails fatigue occurs, fatigue and endurance are not synonymous. Using such a concept of endurance, any fatiguing test protocols that exist cannot therefore be used to measure respiratory endurance. This would suggest that a sub-maximal approach, when no fatigue of a participant occurs, would be more appropriate. The homeostatic response of the breathing control system during a sub-maximal non-fatiguing test, would allow the most efficient breathing pattern to occur. It was found that measuring $\text{InWrs}_{\text{mouth}}$ would best represent this efficiency and as such could be used as an indicator of endurance.

The use of expiratory tidal flow curve analysis was systematically reviewed in 31 journal articles with the most commonly used parameter identified as $t_{\text{TPEF}}$. The work of Colsanti and colleagues was shown to have developed predictive equations of FEV$_1$ from relaxed tidal
breathing using TBPA. Although the literature suggests that the use of the expiratory flow curve is not as sensitive a measure as standard lung function tests, it could provide useful information about the health of the respiratory function again in those situations when standard lung function testing is not applicable or practicable.

A 6-minute trial similar to other sub-maximal exercise endurance tests was developed using a device that was able to apply a R_K that was independent of respiratory air flow. This allowed InWrs^mouth to be measured, a process that was refined through a series of studies. These concluded that for the 6-minute R_K trial protocol, participants should be able to self select their respiratory pattern, the R_K load should be applied throughout the breath cycle and the first minute of data should be disregarded for analysis. The outcome parameters of the 6-minute trial were not seen to correlate with any standard lung function parameters, although as these do not themselves represent measures of endurance, this was to be expected.

The reliability and repeatability of the R_K trial and TBPA was assessed alongside standard lung function tests. It was found that spirometry was the most reliable measure with the smallest coefficient of variation. R_K trials when f_R was unpaced showed lower coefficient of variation than trials when f_R was paced. While spirometry was confirmed as a gold standard measurement, R_K and TBPA trials were found to be both reliable and reproducible measures.

When the R_K trial was assessed during exercise it was found that irrespective of the pattern of breathing or exercise mode, \( \dot{V}_E \) increases with InWrs^mouth in a linear fashion dependent on the R_K load applied. The R_K device therefore would appear able to maintain R_K load irrespective of \( \dot{V}_E \) as claimed by the device’s manufacturers. During exercise InWrs^mouth was seen to increase exponentially with R_K, this would imply that when resistive loads are higher, such as with individuals with increased R_AW, exercise becomes limited because of a reduced respiratory endurance rather than a lack of respiratory muscle strength.

In a similar fashion to healthy controls, COPD patients were able to successfully undertake R_K and TBPA trials. By measuring InWrs^mouth during a standard R_K trial protocol it was possible to detect differences between individuals with chest disease and healthy controls. Additionally TBPA was seen to predict FEV_1 in these patients although it tended to underestimate FEV_1. However if the patients showed a similar pattern of repeatability as that shown with healthy controls TBPA could be used to monitor absolute changes over time.
rather than be used as a diagnostic test.

When comparing children born: at term; preterm; and preterm with CLD, it was found that only FEV₁% pred was significantly different between the three study groups. Spirometry was successfully completed by all although this was most probably due to the level of training provided. An exponential relationship between In(Wrsₘouth and the ability to increase ventilation during maximal exercise was identified that was independent of gestational status. What affect an impaired respiratory status has on this relationship remains unclear. In addition no predictive equation for using TBPA existed for use in children without CF, therefore using the raw data gathered from these 75 participants and linear stepwise regression analysis a TBPA equation was developed for future use.

A novel method to assess the detection of resistive loads was developed using the Rₖ device. This was able to overcome the difficulties associated with the limited existing techniques identified such as the complexity of varying load between breaths and the need to disguise the onset of any load from the participant. Repeatability of detection of resistive loads was good (>90%) in healthy controls when the Rₖ load was over 0.75 kPa.L.sec⁻¹ however it decreased when Rₖ load was below 0.5kPa.L.sec⁻¹. Healthy controls showed a graded decline in the two protocols used when the loads were applied either 1) randomly or 2) sequentially. Despite the intervals between loads being randomly selected in all trials, the decline was slower when the resistances were applied in a sequential order. This suggests that when applied sequentially these healthy participants may have been able to predict or guess when a load may be applied than when the loads were applied in a random fashion. In a limited number of patients with clinically defined obstructive chest disease, data would suggest that these patients are unable to detect Rₖ loads below 0.75kPa.L.sec⁻¹ suggesting that this approach could be used to differentiate between health and disease.

10.2 The Participant
The human respiratory system will always, if allowed, adopt the most efficient breathing pattern for the work imposed upon it. While full cooperation from a motivated participant is required to successfully complete most respiratory tests, not all participants can successfully complete all standard lung function tests. The four main issues that affected this ability were identified as the equipment needed, staff required, the environment in which testing took place and most importantly the participant and the cooperation of the individual being tested.
Minimising these effects is a key requirement when developing tests of respiratory function.

From the review of respiratory endurance articles it was shown how existing tests of respiratory endurance often require participants to continue to fatigue, which can make it difficult to complete. Such tests as these require a motivated and cooperative participant. The review of TBPA articles indicated that it had been used mainly in younger children due to the difficulty in them completing standard lung function tests. It could be suggested that this is because standard lung function tests such as spirometry are seen as being within all individuals’ ability although as argued previously this cannot always be the case.

The 6-minute R\textsubscript{K} trial is similar to other existing physiological tests such as the 6 minute walk test and the Astrand Rhyming Cycle test, for example in terms of length of time and intensity. As both tests are undertaken by both healthy individuals and patients with various forms of chronic disease it was expected that the majority should be able to complete a similar sub-maximal respiratory endurance test.

The development of the R\textsubscript{K} trial showed that all control participants tolerated all seated 6-minute trials, adapting to the R\textsubscript{K} loads within the first minute and entering into a steady state breathing pattern. In a similar fashion these participants successfully completed all TBPA trials. The only exception to this was in exercising R\textsubscript{K} trials when f\textsubscript{R} was controlled, as a limited number of subjects were unable to match their breathing pattern with the pacing required. This suggests that the absence of any paced breathing pattern from the final R\textsubscript{K} protocol is the most suited, allowing individuals to select their most efficient breathing pattern, resulting in the best representation of their ability to endure an R\textsubscript{K} load. When breathing pattern is self-selected all participants are able to complete 6-minute trials, some even while exercising at intensities of up to 150 watts, and R\textsubscript{K} loads of 1.5 kPa.L.sec\textsuperscript{-1}.

COPD is a common disease nationally and is a particular health issue in Rhonda Cynon Taf which has one of the highest standardised mortality ratios for chest disease in the UK. During discussions with COPD patients as part of clinical studies and outreach work it was found that these patients were keen to take part and get involved with research into their condition. When asked many of these patients stated how they found completing maximal spirometry manoeuvres difficult, further confirming the need for alternative sub-maximal methods of assessing respiratory function.
It was identified in the literature that children often required substantial coaching to complete the tests required of them. During the study of children in this thesis a large period of time was devoted to training to complete FEV\textsubscript{1} manoeuvres which resulted in a 100% success rate. The level of instruction for both R\textsubscript{K} and TBPA trials was substantially less which perhaps explains the lower rate of successful outcomes. However such approaches to R\textsubscript{K} and TBPA trials reflects how such trials may be used without strict instruction away from specialist clinical environments.

Using a novel approach to assess resistive loads detection, all participants were able to complete all trials with relatively little training. Substantial mental cooperation was required in terms of concentration but the trials themselves required comparatively little physical effort. A graded decline was observed in healthy controls, but patients with obstructive disease showed a rapid decline, with none able to detect R\textsubscript{K} loads below 0.75 kPa.L.sec\textsuperscript{-1}.

### 10.3 Summary

This thesis describes how I developed and used new and existing technologies to provide new methods for sub-maximally assessing respiratory function. These methods were successfully applied in healthy controls at rest and while exercising, in children and patients with COPD.

In Chapter 5 it was hypothesised that R\textsubscript{K} trials and TBPA would be both repeatable and reliable measures. In a series of small scale studies it was shown that Spirometry showed the greatest level of repeatability which confirms its status as a gold standard measure. While not as repeatable as spirometry, both R\textsubscript{K} trials and TBPA showed a sufficient level of repeatability to make them a practical alternative in the situations identified when existing techniques like spirometry would not have been practicable, confirming the experimental hypothesis. At rest in healthy participants InWrs\textsuperscript{mouth} was observed as 0.33 (±0.08) J.L.

In Chapter 6 it was hypothesised that increases in ventilation due to exercise results in increases in InWrs\textsuperscript{mouth}. During R\textsubscript{K} trials at rest and during exercise irrespective of the pattern of breathing or exercise mode, ventilation increased with InWrs\textsuperscript{mouth} in a linear fashion dependent on the R\textsubscript{K} load applied. This confirmed the experimental hypothesis. When ventilation was constant, InWrs\textsuperscript{mouth} was shown to increase exponentially with R\textsubscript{K} indicating how an increased resistive load, similar to that in patients with obstructive chest disease, would have a greater limiting effect.
In Chapter 7 it was hypothesised that $R_K$ trials and TBPA would be able to differentiate between healthy individuals and patients with COPD. When completing an $R_K$ trial, COPD patients had an $\text{InWrs}_{\text{mouth}}$ of $0.40 \pm 0.15$ (J.L) $20\%$ greater than that reported for healthy controls confirming the experimental hypothesis in terms of $R_K$ trials. TBPA was dependent on knowing the respiratory status of an individual to apply the correct predictive equation. However when the appropriate TBPA equation was applied it provided quantitative measure of airway obstruction that could be used to provide a surrogate measure of $\text{FEV}_1$ confirming the experimental hypothesis. This suggests that in its present form that TBPA in not capable of differentiating between health and disease without knowledge of an individuals respiratory status diagnosed by spirometry for example. However TBPA may provide a suitable alternative to existing measures in environments such as home monitoring when its ease of use and analysis could provide an advantage.

In Chapter 8 it was hypothesised that $R_K$ trials would be able to differentiate between children born preterm, preterm with CLD and at full term. As has been shown in previous studies $\text{FEV}_1$ was significantly lower in preterm children. In a similar manner to measures of height, weight and physical fitness, there were no differences in $\text{InWrs}_{\text{mouth}}$ between the three experimental groups, rejecting the experimental hypothesis in terms of $\text{InWrs}_{\text{mouth}}$. Although significant differences were found between the groups in terms of $\text{FEV}_1$, suggesting some form of greater airway obstruction in children born preterm, the severity of this obstruction was not as great as that seen in COPD patients. The children in the preterm CLD group had a $\text{FEV}_1\%_{\text{pred}}$ $81\% \pm 14$ which in terms of GOLD classification of COPD (Table 7.1) would put them on the cusp of mild COPD ($\text{FEV}_1\%_{\text{pred}}<80\%$). This would suggest that $\text{InWrs}_{\text{mouth}}$ is much less sensitive a measure than spirometry and is only able to detect greater differences between health and disease.

In Chapter 9 it was hypothesised that a resistive detection method using $R_K$ loads could differentiate between healthy individuals and COPD Patients. Healthy individuals showed a graded decline in their ability to detect $R_K$ loads. In contrast in the limited number of COPD patients who undertook trials were unable to detect loads below $0.75 \text{ kPa.L.sec}^{-1}$. This suggests that this method could be used to differentiate between health and disease confirming the experimental hypothesis.
Chapter 11 – Thesis Conclusion

11.1 Accuracy of Respiratory Measurement

Spirometric Assessment of FEV$_1$ was shown to be the most reliable and accurate measure of lung function in all the participants groups assessed, as was expected and discussed earlier (Section 1.0). As has been argued throughout this thesis there are occasions when this method of testing is neither practical nor applicable, such as when assessing children, when patients are exacerbating or when these tests are used outside of a controlled clinical environment. A need for new approaches to assessing respiratory function to overcome these and other issues was identified. This raises the question; Can such new methods, particularly those that use a sub-maximal approach to assessing respiratory function, be as good as existing techniques?

There exists a trade-off when using any method that assesses respiratory function between the level of accuracy required and the level of test sophistication involved (Figure 11.1) which is dependent on the required outcome of the test, whether for diagnosis, screening or monitoring. Test sophistication encapsulates the four factors identified earlier (Section 1.6) as being key to overcoming the potential for error in tests of respiratory function. The level of these factors (either individually or concurrently) has a direct effect on the accuracy of a test.

![Figure 11.1: Effect of Test Sophistication on Test Accuracy.](image)

When a test has a high level of sophistication the factors that can contribute towards error are rigorously controlled or negated. Using an invasively taken measurement of oesophageal pressure to assess respiratory muscle function for an example requires: 1) a high level of participant cooperation; 2) to be conducted in a highly developed clinical environment; and
3) with well trained staff could be expected to achieve a highly accurate result, such as Point A on the continuum (Fig 11.1). Note that even in this situation it would not be expected to be 100% accurate or precise, due to the inherent variability when testing a biological system.

Conversely for a test with a low level of sophistication the chance of these negative factors occurring are magnified. Using a peak flow test being conducted in a home environment with a simple peak flow meter for an example would mean: 1) No trained staff to check technique or the status of the machine; 2) and would still require maximum effort on behalf of subject, providing a result of questionable accuracy. While if correctly conducted such a test may provide valid, clinically reliable results it could also result in a test where one or more sources of error invalidate any test outcome. This would be represented at a point anywhere between A and B on the continuum (Fig 11.1) making any accurate interpretation difficult to achieve. There exists then a point where the level of test sophistication is such that it is questionable whether there exists any benefit from conducting tests as the level of accuracy is unreliable and not clinically usable, represented to the right of Point B on the continuum (Fig 11.1).

The work of this thesis has been to investigate and develop new methods of assessing respiratory function that fall between Points A and B. In that they may not have the accurate diagnostic ability of existing tests that are highly sophisticated but that they are able to reliably and repeatedly provide important clinical information about an individual’s respiratory system in a test that has a lower level of sophistication requiring less effort on behalf of a participant and reduced clinical oversight.

The aim of this thesis was to investigate and develop such new methods of assessing respiratory function focussing on two techniques 1) Measurement of respiratory endurance and 2) Predicting FEV₁ from relaxed tidal breathing. From this work a third technique was developed by combining the two devices so that the ability to detect resistive loads could be assessed.

11.2 Key Findings

Using a sub-maximal 6-minute trial which applied an $R_k$ load, $InWrs^{mouth}$ was measured which was used as an index of respiratory endurance. This was found to be higher in patients with COPD (described in Chapter 7) indicating that it could be used to differentiate between
health and disease. However in 8-12 year old children (Chapter 8) despite significant differences in FEV$_1$%pred between children born at term and preterm with CLD, no differences was seen in InWrs$^{\text{mouth}}$. While some children did show a decreased FEV$_1$ this was not of a similar magnitude to that seen in COPD and it may indicate that such techniques may only be useful in screening individuals with pronounced airway obstruction.

TBPA was seen to predict FEV$_1$ in controls and COPD patients although this was not as sensitive as spirometric measurement of FEV$_1$ (Chapter 7). The use of two predictive equations meant that it was necessary to know the respiratory status of an individual before assessment which would prevent its use as a simple screening device. There is a need to further develop this predictive TBPA work into one single equation which is explored below.

By adapting the R$_K$ device and using it conjunction with the pneumotachograph used for TBPA a protocol was developed that was able to assess a participant’s ability to detect resistive loads (Chapter 9). The ability to detect such loads may be able to act as an objective measure of breathlessness. While healthy controls showed a graded decline in detected R$_K$ loads as they were reduced from 1.5 to 0.15 kPa.L.sec$^{-1}$, COPD patients were unable to detect any R$_K$ loads below 0.75 kPa. L.sec$^{-1}$.

11.3 The meaning of the tests in terms of physiological variation between individuals.

It was expected as detailed in section 10.0 to find differences in R$_K$ trials in individuals on the basis of their lung health, in this context on the basis of FEV$_1$ as a marker or airway obstruction As discussed previously TBPA required the existing respiratory status to apply the correct analysis equation, which controlled for physiological variation due to age and height (Section 3.2.1).

In a similar way when performing R$_K$ trials, the outcome measure, InWrs$^{\text{mouth}}$ was scaled for physiological variation between individuals by expressing the energy used per litre of inspired breath. This took into account the variability in tidal volume and breathing rates seen between individuals. For example an individuals with a high f$_R$ and low V$_E$ (such as a child) compared to an individual with low f$_R$ and high V$_E$ (such as an adult) may have the same InWrs$^{\text{mouth}}$. This meant for example that InWrs$^{\text{mouth}}$ at rest seen in healthy adults (Chapter 4) was similar to that seen in healthy children (Chapter 8) despite substantial differences in height and age.
When testing human participants some form of variation is unavoidable and participants in particular sub-groups, eg COPD patients in Chapter 7 and the term/pre-term children in Chapter 8 were carefully selected. Furthermore as only patients with clear common pathology (COPD) were recruited the work within this thesis is unable to provide any inference on the techniques described ability to differentiate with other lung diseases.

While the TBPA equations were designed to take age and height into account $\text{InWrs}^{\text{mouth}}$ currently does not. This was in part due to the limited number of participants, 174, who displayed a wide range of age and respiratory health status assessed during this thesis. This in turn would preclude investigation into any effect physiological differences; age, gender, height etc, may have on $\text{InWrs}^{\text{mouth}}$. Further work would allow the opportunity to develop predictive equations for this parameter from which the variation of diseased values could be gauged.

11.4: Validity of new methods when there are no new obvious means of comparison

Within a research paradigm scientific exploration progresses by the comparison of new techniques and methods with those that already exist and have been shown to be valid and reliable. New techniques have to show some advantage over existing techniques whilst maintaining a similar level of validity and reliability. TBPA was developed as a method to predict $\text{FEV}_1$ (as measured by spirometry), which provided a gold standard for it to be compared with. It was shown that spirometry was the more reliable and sensitive measure and the use of TBPA was also confined by the need to be aware of an individuals respiratory status to apply the correct predictive equation.

It is the inherent difficulty with the work of this thesis that the $R_K$ trial developed cannot by its very nature be compared to existing techniques, specifically because of the difficulties identified in the definition of endurance and existing methods to measure it. What this thesis sets out in terms of respiratory endurance is a different paradigm as to what is endurance is and how it should be measured.

Therefore the work of thesis initially focussed on developing a reliable and repeatable measure (Chapter 4-5) and then testing this against a series of experimental hypothesis (Chapter 6-9). In essence the gold standard was this repeatable measure that the work undertaken was compared to in the experimental chapters in the latter half of the thesis.
This research paradigm was to assess whether a difference could be detected where it would be reasonable to hypothesise that one existed, for example between healthy individuals and those with obstructive chest disease, and at rest and during exercise. By testing these hypotheses and detecting a difference would show that the Rₖ trials are valid, even if it were not immediately clear what these differences mean or why they occur. The experimental hypothesis in terms of health and disease assume these differences on the basis of existing respiratory status although this may not be the case, and could be due to lack of physical fitness or de-conditioning for example. However without a gold standard measure of endurance what they do not show is that they are able to measure respiratory endurance per se.

This difficulty could be overcoming by undertaking 6 minute Rₖ trials whilst internally assessing oesophageal pressures to calculate work of breathing, a technique described previously (ATS 2002) which would allow the effect of Rₖ loads to be assessed. This could allow a means of direct comparison between the work of breathing measured by internal pressure change against InWrsₘouth and whether the differences observed in the experimental chapters could be replicated. Due to practical constraints primarily the lack of sophisticated equipment and technical and medical support required, this type of investigation was beyond the scope of the work undertaken within this thesis.

11.5 Advantages / Disadvantages of the Techniques Described
Both the Rₖ and TBPA trials were undertaken by individuals of a wide range of ages and respiratory status, in a variety of modalities including whilst seated, and exercising at intensities with work rates up to 150 Watts. As a result of these trials there were no adverse events and participant safety was not compromised. On the limited occasions when Rₖ trials were halted early this was during protocols when fₚ was paced and participants could not maintain required rate. During Breathlessness Sensitivity trials none were halted early and healthy participants and COPD patients were able to successfully complete them all. Therefore all three methodologies would appear simple and safe to undertake.

The length of Rₖ trial was used as it was a similar length to existing sub-maximal exercise tests although anecdotally this was felt by some subjects to be a long time. When compared with some methodologies identified in the synthesis of existing methods however 6-minutes was a relatively short trial length. This raises questions of a participant’s comfort and
willingness to complete longer protocols such as MSVC trials when maximal effort is required that while usually 15-minutes in length, could be as long 150-minute (Section 3.1.3). In this context a shorter test could be better in maintaining participant motivation and willingness to complete. The early development work of the $R_K$ trial showed that a steady state breathing pattern was achieved within the first minute (Section 4.1), so that the 6-minute trial could be reduced in length such as the 3-minutes used in TBPA. The length of Breathlessness Sensitivity trials was governed by an individual's $f_R$ as all participants had to complete the same number of breaths, allowing participants to self select $f_R$ which may have had a positive effect on cooperation during the trial. With the concentration needed during the trial however it would be difficult to introduce a system of controlling $f_R$ without it affecting the trial.

The use of bespoke software analysis of the data output of TBPA removes the potential for human error when selecting tidal breathing curves for analysis. As was identified, previous techniques relied upon study investigators selecting the best flow curves which may be suitable for use in small scale research studies but would preclude its clinical use. Furthermore another significant advantage of the bespoke software is its potential to speed up the analysis process allowing the simple data files generated to be quickly processed. Currently the output of this analysis is rudimentary although it would require only a small amount of development work to produce a polished TBPA outcome report.

The Breathlessness Sensitivity device that was developed has many advantages over the older techniques that were described in Chapter 9, principally the ability to electronically control a trial, varying the resistive loads between breaths without halting a trial or giving any indication to a participant when this may be about to happen. The equipment while cumbersome was able to be used with relatively little training by both healthy controls and COPD patients although how sensitive the device is between smaller changes in $R_K$ load needs to be explored. By using $R_K$ as the resistive load it represents a more natural flow independent resistance that could be better than using fixed resistances that are flow dependent.

11.6 Sophistication of $R_K$ trial, TBPA and Breathlessness Sensitivity
Of the three techniques breathlessness sensitivity would have the highest level of sophistication as it requires a trained operator to complete the trial and as such can only be
used within a clinical setting. In addition the high level of concentration necessary would preclude its use in all but the most cooperative of participants, this would be possible for example in children. However the low levels of physical effort required would mean that it could be used in those situations when maximal testing is not possible and it may provide a useful and simple way of objectively measuring breathlessness. When placed on the continuum described previously (Fig 11.1) it would be placed towards Point A at T1 (Fig 11.2).

Both the Rₖ trial and TBPA would have a lower level of test sophistication, and it would be possible for participants to conduct these tests without any assistance or requirement for a test operator. The removal of the requirement for maximal effort from these methods reduces the effect on the accuracy of these tests and as such would be represented at Point T2 on the sophistication continuum (Fig 11.2).

![Accuracy](image)

**Test sophistication**

**Figure 11.2: Sophistication of Rₖ trial, TBPA and Breathlessness Sensitivity**

11.7 Future Work Building on That in This Thesis

The work in this thesis could be used as the start point for future work in the following ways:

11.7.1 Technical Development

*TBPA*

As more adult data is collected this can be used to develop a single predictive equation, which removes the need to know the respiratory status of an individual before they are assessed. Such an equation could then be used to provide a simple technique to screen
individuals to identify those who may require further specialist respiratory testing, streamlining and improving the delivery of respiratory function assessment services.

Using the raw flow data from the children cohort (Chapter 8) a new predictive equation using TBPA was developed as part of the work of thesis which would require a prospective study using this to estimate its predictive ability. The accuracy of spirometry was clearly shown in this thesis and this was again shown in these children, although this was undoubtedly due to the high level of instruction and support given to individual children to ensure a valid result was achieved. Such intense support is not always practical for example home monitoring of children with asthma or those with cystic fibrosis. Could TBPA analysis be able to provide a simple method of monitoring lung function for these patients? Early detection of a decline in lung function could be a useful way of preventing the onset of disease exacerbations which have both a considerable impact on quality of life and financial impact on the health service.

**Repeatability**

Currently the repeatability work described (Chapter 5) was conducted only in healthy adults who do not represent the groups most at need of new sub-maximal test, patients with chest disease, children etc. Therefore there needs to be further work looking at the repeatability in specific groups and environment within in which they would be used.

**Combining the techniques into one device?**

Currently the devices used for all three methods are too big and cumbersome to be used in any practical way, performing more as proof of concept devices. The technology used though is relatively simple and could be scaled down into more appropriate devices although this would come with inherent work and cost involved. If this could be undertaken it would be beneficial to combine the technologies into one device that would be able to complete all three methodologies. Alternatively a family of devices could be developed with increasing complexity and cost for a range of uses i.e. from home testing, primary care assessment in GP surgeries and pharmacies through to tertiary care on inpatient wards and in specialised respiratory function centres. This would be in a similar way to the development of standard spirometers that are found in all these environments.

**11.7.2 Clinical Use**

*Home monitoring, Tele monitoring, Emergency Monitoring*

TBPA and R\(_K\) trials could be particularly useful in clinical groups where large changes in respiratory function occur rapidly with the onset of disease such as in exacerbations of CF or
COPD. Either of these techniques could be used as an early indicator of decreased function particularly when assessed in a home environment away from specialist testers or equipment. Previously the thesis author has worked with telemedicine in COPD (Lund et al. 2009) where it was found that while patients could easily master the electronic diary element of the study the biggest issue was the correct measurement of respiratory function. A simple test that could replace FEV$_1$ measurement and still provide useful information either as FEV$_{1TAP}$ or InWrs$^\text{Mouth}$ would be useful.

**Preterm Children**

Further study of this cohort could provide useful information about how children born prematurely develop as they grow. For example do the differences in FEV$_1$ shown continue into adulthood? Could there be a link between prematurity and respiratory disease in later life? Should such children be specifically targeted to prevent behaviours that may adversely impact their respiratory health such as tobacco smoking and environmental exposures?

**Breathlessness Sensitivity**

It would be interesting to assess the ability to detect resistive loads in terms of breathlessness status as this could provide an objective measure of breathlessness. While this thesis has shown the concept for using R$_K$ load to assess resistive detection more work is needed to quantify the exact load increments and protocol design. Furthermore bronchodilators could be used in a similar way to a standard salbutamol challenge test with the Breathlessness Sensitivity method described. In a standard salbutamol challenge test with a 15 minute gap between drug administration and spirometric assessment there would be time to conduct a sensitivity trial.

**11.7.3 Exercise**

Whether the ability to overcome a high R$_K$ load is dependent either on fitness levels (and motivation) or upon inherent respiratory function has yet to be investigated. With the increased use of pulmonary rehabilitation programmes it is necessary to monitor endurance performance rather than strength. Valid measures of endurance are thus needed to assess the outcomes of such interventions (Powell and Williams 2009). Despite intense investigation the importance of respiratory muscle endurance in the failing patient or the obstructed patient during exercise is still relatively inadequate. The R$_K$ protocol was able to differentiate between healthy individuals and those with COPD although the effect of exercise on InWrs$^\text{mouth}$ in COPD patients would be a valuable finding. For example how does InWrs$^\text{mouth}$ change during a 6-minute walk test? In healthy subjects there appear no obvious contra-indications for COPD patients to complete R$_K$ trials whilst completing sub-maximal exercise.
Furthermore calculating $\text{InWrs}^{\text{mouth}}$ could provide additional useful information about a patient’s respiratory endurance capability alongside their exercise endurance.

11.8 The Thesis in Summary

The difficulties with lung function assessment are well established and have been described in this thesis. Much recent emphasis has been put on developing existing devices and protocols rather than developing new techniques and approaching these difficulties from alternative viewpoints. This thesis has described the development of three innovative methods to assess the function of the respiratory systems that aim to overcome the issues associated with maximal testing. It has been shown that they are easy to undertake for a range of participants, simple to analyse and are able to reliably differentiate between health and disease, suggesting that they could become a useful adjunct to existing methods of respiratory assessment.


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Appendix 2.1: Respiratory Endurance Review
Appendix 2.2: TBPA review
Appendix 3.1: UK and EU patent applications
Appendix 7.1: COPD Questionnaire
Appendix 7.2: Sample study protocol.
### ‘Respiratory Muscle Endurance’

<table>
<thead>
<tr>
<th>Author</th>
<th>Term</th>
<th>Stated Definition</th>
<th>N=</th>
<th>Subject</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>A25</td>
<td>1. Respiratory muscle endurance (RET)</td>
<td>RET = sustained</td>
<td>30 (19M)</td>
<td>COPD patients</td>
<td>1. based on 12 sec MVV, x 3 highest recorded. RME = time of sustained ventilation at 66% of highest MVV. No coaching or paced breathing although VE feed back given. Normocapnia maintained. If &gt;15mins repeated at 75% of MVV. 2. IME inspiratory threshold loading, (Nickerson &amp; Keens) start at 20% of P_{Imax} increased every 2min by 50% of inital weight until subject unable to continue. greatest weight sustained for 1 min = IME. Test repeated 3 times.</td>
</tr>
<tr>
<td></td>
<td>2. Inspiratory muscle endurance</td>
<td>RMT</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>A42</td>
<td>Respiratory Muscle Endurance</td>
<td>RMT</td>
<td>28 (16M)</td>
<td>Healthy sedentary</td>
<td>Breath at Ve corresponding to 70% MVV (fb paced by metronome)for more than 2 mins. If &lt; 2mins Ve reduced to 65% and trial repeated. Performed a breathing endurance test to exhaustion(determined by Ve having dropped by &gt;10% below target or by subject stopping) at the Ve previously established.</td>
</tr>
<tr>
<td>A56</td>
<td>Respiratory Muscle Endurance</td>
<td>RET=exhaustive</td>
<td>14 (11M)</td>
<td>8 = paraplegia</td>
<td>RET assessed using SpiroTiger. Device set at 20, 40 or 60% of individual MVV in random order over 3 sessions at least 72 hrs apart. Familiarised with normocapnic hyperpnoea technique. Encouraged to maintain target Ve, test halted on exhaustion or if Ve = &gt;5L/min lower than target for 30 sec or test lasted &gt;60min.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>normocapnic</td>
<td></td>
<td>6 = tetraplegia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>hyperpnoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A131</td>
<td>Respiratory Muscle Endurance</td>
<td>1. IME = maximum</td>
<td>99 (50M)</td>
<td>Healthy sedentary</td>
<td>modified Martyn and Nickerson &amp; Keens was applied. Before test, subjects trained with 100-gram insp load for 60 s. Subject synchronized fb with pacing. fb were monitored . Subjects breathed at 0 load for 2 min. 100-gram weight added every 2-min. At end of each 2-min, subject breathed without loads for 2 min. Heaviest load tolerated for 2 min was recorded as Cmax load expressed in grams.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tolerated load for a 2min incremental Martyn test (C_{max})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. time of sustained breathing against an inspiratory pressure load equivalent to 80% of C_{max}</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Age groups:**
- 1 = 20–29 years;
- 2 = 30–39 years;
- 3 = 40–49 years;
- 4 = 50–59 years;
- 5 = 60–70 years

Subject breathed with load of 80% of Cmax until threshold pressure for 3 consec breaths ceased to be generated (exhaustion)= Time that elapsed from start of test to exhaustion (Tlim). Cmax and Tlim protocols were repeated 2 times by each subject on the same day, with a 20-min rest between each test. The inspiratory time ratio (T_{I}/T_{TOT}) was kept constant. The respiratory rate was approximately 20 breaths per minute.
| A132 | Larson et al 1999 | Respiratory Muscle endurance | COPD prior to 3 week pulmonary rehab | Discontinuous incremental threshold loading (DC-ITL) test modification of Nickerson & Keens, = 3-min stages, 2-min work followed by 1-min rest. During 1st stage, breathed against ITL=30% of Pimax, load increased 50g for each subsequent stage. RME expressed as relative maximal load, defined as peak mouth pressure during last completed stage divided by the Pmax, measured at beginning of each visit (Rel mouth pre) and as Absolute maximal load defined as inspiratory pressure at mouth during last completed stage of the test (Ab mouth pres) and weight added (ITL wei) During rest interval, patients released mouthpiece to clear saliva, cough, drink water Patients replaced mouthpiece approx 10 s before restart. In addition, patients were vigorously coached to continue breathing against ITL until fatigue |
| A138 | McElvaney et al 1989 | Respiratory Muscle Endurance | Normal healthy | RME measured using a 1) 2-min incremental threshold loading protocol (Martyn) weighted, subjects started at 100 g and 100 g weights added at 2 min intervals. Subjects continued until no longer inspire after 2-3 unsucc attempts before end test. Tests repeated x3 with ≥24 hrs between. Heaviest load tolerated 2 min= max load. 2) Maximal loading protocol on 3 occasions. 1-min inspired against half highest max load = ITL test as warm-up, then against max ITL load until exhaustion. Length of time subjects could inspire against their max load was endurance time (tim). |
| A152 | Koppers et al 2006 | Respiratory Muscle Endurance Capacity | Inspiratory muscle endurance test, Hypernea endurance test | RMT | COPD awaiting pulmonary rehab prog | 1) IME measured by incremental threshold loading (Nickerson & Keens). Patients inspired against a weighted inspiratory valve, increased at regular intervals. Pressure achieved during heaviest load tolerated for at least 45 s was defined as maximal sustainable inspiratory pressure (Pismax) 2) HET assessed endurance performance of respiratory muscles. Subjects breathed in a closed spirometer circuit to maintain an isocapnic situation during the test. Oxygen was supplemented. Patients breathed with a fixed IB= 30 duty cycle =0.33 using an electronic metronome and TV 45% of VC. Given visual feedback of TV and were not encouraged. Test terminated when patient not sustain the IB or TV during 3 consec breaths or after a max of 20 min, and time was recorded (seconds) |
| A153 | Mador et al 2005 | Respiratory Muscle Endurance | RMT | COPD starting pulmonary rehab | RME tested using same device used during hyperpnea training. V' e, end-tidal CO2 (Petco2), and O2 sats continuously monitored. Subjects maintained a target V' e of 70% of the 12-MVV. (MVV measured x3 best result chosen). When target V' e no longer maintained test halted and endurance time calculated. RME measured x3 and longest endurance time was chosen |
| A154 | Winsberger et al 1997 | Respiratory Muscle Endurance | RME time = max time (sec) subject sustain breathing against inspiratory pressure load=70% of individual Pimax | 36 (18 M) | 18 = sarcoidosis, 18 = control matched age and gender | RME assessed by measuring the endurance time using a modified threshold loading device as designed by NICKERSON & KEENS. Expiration can be performed without any resistance. First warmed up against an inspiratory pressure load = 15% of Pimax during 2 min. Then breathe at 70% Pimax until test fatigue/exhaustion. Test terminated if RME time > 15 min. |
| A156 | Rassler et al 2007 | Respiratory Muscle Endurance | RMT | 10 (4M) | Myasthenia Gravis | RME assessed x2-3, Using RMT device connected to a metabolic cart. Instructed to breathe 25–40 per min with a VT between 50% and 75% of VC to induce test termination due to task failure after max of 10–12 min, encouraged them to breathe faster or slower if necessary. Criteria to terminate test = patients’ perception of exhaustion or a reduction in ventilation by >10% of target for 1 min. Measured endurance time (TLim: time until test termination) and endurance volume (VLim: total ventilation during test, calculated as TLim multiplied by average V̇E). |
| A157 | Matecki et al 2001 | Respiratory muscle endurance | 20(M) | 10 = Duchenne muscular dystrophy, 10 = control age & sex matched | RME measured by max time against load = 35% Pimax at FRC, so time would approx range from 3-10min. Period of loaded breathing defined as endurance time (Tlim) |
| A159 | Koechlin et al 2005 | Respiratory Muscle Endurance | RME = max time Tlim a subject is able to sustain a specific submaximal muscle task | 29(14M) | 15 = pre- peri pubertal, 14 = near the end of the pubertal process (defined by Tanner stages) | Standardized method of RME in healthy and DMD children (Mateki 2001) Pressure threshold test to assess time limit (Tlim), Nickerson & Keens at 50% Pimax, Ti/Ttot equal to 0.5. Measurements of Pimax and breathing pattern used to calculate tension-time index of respiratory muscle, TTI, product of mean pressure developed by respiratory muscles in relation to maximal capacity (Pm/Pimax) and duration muscle contraction in relation to duty cycle. Children had to produce 50% Pimax, with Ti/Ttot =0.5, their tension-time index, TTI (Pm/Pimax . Ti/Ttot) estimated = 0.25. |
| A161 | Laghi et al 2005 | Endurance of the respiratory muscles | 21(M) | COPD, 11= Hypogonadal, 10= Eugonadal | No detailed methodology refers to A182. Similar device to Nickerson & Keens, inspiratory threshold test.Weights added so that initial Pth (negative threshold pressure) subjects had to generate was 40% MIP Every 2 min weight increased by 10% of MIP, end of test = failure of the subject to sustain the breathing task. No instructions given to subjects regarding breathing pattern. Max Pth was defined as inspiratory pressure developed with each breath at highest load at which ventilation could be sustained for 230 s. |
| A163 | Chang et al 2005 | Inspiratory Muscle Endurance | Fatigue Resistance Index = FRI | 20 (11M) | Patients who had received mechanical ventilation for ≥ 48 hrs | Patients breathed through an inspiratory resistance that was equivalent to 30%* initial measurement of Pimax for 2 min, Pimax was recorded every 30 seconds. FRI = final Pimax/initial Pimax |
| A164 | Koessler et al 2001 | Respiratory Muscle Endurance | RMT | 27 | 18 = Duchenne Muscular dystrophy 9 = spinal muscular atrophy | 12s MVV used as parameter for RME. Repeated x3 best trial used. A = VC 27 – 50% pred B = VC 51 – 70% pred C = VC 71 – 96% pred |
| A165 | Weiner et al 1992 | Respiratory Muscle Endurance | RMT | 30 (12M) | Moderate to severe asthma (ATS guidelines) | To determine IME, a device = Nickerson & Keens used. Inspiratory work was increased by addition of 25- to 100-g weights at 2-mm intervals, (Martyn) until subjects were exhausted and no longer inspire. Pressure achieved with heaviest load (tolerated > 60 s) defined as peak pressure (Ppeak). RME = Ppeak/Pimax % |
| A166 | Nava et al 1992 | Respiratory Muscle Endurance | Endurance time | 15 | COPD >20% reduction of pred values | Used a tube with adjustable orifice so inspiratory resistance = 70% baseline MIP, fB 20 bpm, ti/tot 0.4. fatigue time = point when target pressure could not be maintained 4 breaths |
| A167 | Lake et al 1990 | Respiratory Muscle Endurance | Severe Chronic Airflow obstruction | 28 (24M) | FEV1 = 32% pred | Randomized to either control or 4 intervention groups. RME = inspiratory loaded breathing modified Nickerson & Keens and Martyn. 1) inspired against a load which was increased by 2.5 – 10 cm H2O every 2 mins for as long as tolerate. 10 min rest 2) Inspire against load = 60% MIP until fatigue – sec. Halted if reached 10min. |
| A168 | Morrison et al 1989* | Respiratory Muscle Endurance | Healthy normals | 10 (5M) | RME measured using 2 min incremental threshold loading test modified Nickerson & Keens. Ppk with each breath and Pmean during the whole respiratory cycle were recorded. Subjects began 2 min incremental test, at a low load (100 g) and 100 g added every 2 mins until could not continue. Only weights which could be tolerated for full two minutes were used to calculate max. Average Ppk (generated over six breaths), Pmean, VT, VE, Ti and Pr for each breath were recorded for each weight. Max values of Ppk, |
Ppk/MIP, Pmean and max load were used as measures of RM endurance. Subjects tested at fB of self chosen, 6, 12, and 20 breaths per minute. Subjects were free to choose Ti and VT.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Title</th>
<th>Cond.</th>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morrison et al 1989</td>
<td>Respiratory Muscle Endurance</td>
<td>RME= MSVC = Maximal Sustainable ventilatory capacity = is the highest ventilation that can be sustained for 15 min.</td>
<td>16 (11M) 8 = COPD 8 = healthy age matched</td>
<td>RME measured using 2 min incremental threshold loading test (Nickerson &amp; Keens). Ppk with each breath and Pmean during the whole respiratory cycle were recorded. Subjects began at 100g and 100g added every 2 mins until not continue. Last weight tolerated for full two minutes were used to calculate max. Average Ppk (generated over 6 breaths), Pmean, VT, VE, Ti and Pr for each breath were recorded for each weight. Max values of Ppk, Ppk/MIP, Pmean and max load were used as measures of RME. Tested at fB of self chosen, 6, 12, and 20 bpm. Ti and VT uncontrolled</td>
</tr>
</tbody>
</table>
| Sonne et al 1982   | Respiratory Muscle Endurance | RMT    | 6(?) no gender | COPD FEV1 <35%Pred

In results: RME was measured by the amount of inspiratory resistance that could be tolerated for 10 min, indicated by diameter of inspiratory orifice tolerated. |

| Orenstein et al 1981 | Respiratory Muscle Endurance | RMT    | 31 no gender after drop out | CF

RME measured in nine exercise and eight control by modified of Leith & Bradley and Keens, assessed by MSVC. Patient breathed at 90% Maximum breathing capacity. End-tidal gas monitored. Not all patients were able to maintain ventilation at 90% MBC, were allowed to continue at highest sustainable level above 65% and up to 90% MBC for as long as possible or 15 min, whichever came first. Scores were assigned in "sustained hyperpnea" (SH) units, by multiplying % of MBC achieved by the time in min for which it was sustained. Thus a patient who performed at 70% of his MBC for ten minutes earned an SH score of 700 SH units. |

| Holm et al 2004     | Respiratory Muscle Endurance | RMT    | 20 (16M) Triathletes or experienced cyclists | RME assessed using SVC test similar to Leith & Bradley. 3 min warm up period (at approx 80% MVV) preceded all tests. for a test to be included in the final analysis, VE during the first 30 breaths of the test had to be greater than or equal to the subjects MVV to ensure that the effort was maximal. average VE during the plateau phase (over the last 2–3 minutes of the test) was taken as the SVC. SVC from two tests had to be within 10% of each other and this was considered a baseline measurement to which all subsequent SVC tests were compared |

<p>| Boussana et al 2001 | Respiratory Muscle Endurance | RME = is the property of respiratory muscle that affords resistance | 12 (M) Competitive triathletes | RME assessed by Tlim = the maximal time a subject can breathe against a predetermined inspiratory submaximal load. Set at 75% PImax at FRC at each inspiration. Subjects fB controlled by electronic metronome rate at 30-min. 1, in order to reproduce the respiratory cycle at rest (Ttotrest _ 4 s) with Ti/Ttot _ 0.5. Loaded breathing continued until subject... |
| A175 | Weiner et al 1998 | Respiratory Muscle Endurance | Inspiratory Muscle Endurance | 21 | no gender | Obese mean BMI 41.5kg/m² | To assess IME used a similar device to Nickerson &amp; Keens, inspiratory elastic work increased by 25-100g weights at 2 min intervals = Martyns, halted on exhaustion no longer able to continue. Pressure achieved with the heaviest load tolerated for at least 60 sec defined as peak pressure PmPeak. RME defined as ratio PmPeak/Pimax % |
| A176 | Uijl et al 1999 | Inspiratory endurance capacity of the respiratory muscles Pendu | Respiratory Muscle Endurance | RMT | 9 (8M) | Tetraplegia at C3 –C7 | Endurance capacity or fatigability of RM assessed by Incremental threshold loading test (Martyns), 10 – 40g weights added every min aimed at achieving max protocol within 20min. Highest pressure achieved and maintained for 1 min defined as Pendu. |
| A177 | Chatham et al 1996 | Respiratory Muscle Endurance | RMT | 10(5M) | normal | Test of RME ‘TIRE’ at 80% of sustained maximal inspiratory effort ‘SMIP’. Followed pressure template, failure to achieve at least 90% = end of test. RME was assessed using point of TIRE failure expressed in total pressure time units |
| A178 | Mancini et al 1995 | Respiratory Muscle Endurance | RMT | 14 | no gender | Congestive heart failure | RME assessed by incremental MSVC test where target flow increased every 3 min until failure to maintain target. Iscopania maintained throughout. Begin at 20% MVV, 10% increase every 3 min to a maximal tolerated level, MSVC defined as highest workload completed for a full 3 min. |
| A179 | Supinski et al 1985 | Respiratory Muscle Endurance | | 12(8M) | Normal University students | RME assessed modified Nickerson &amp; Keens from the time to exhaustion while subjects inspired against massive inspiratory threshold loads (54-140 cmH2O), by adding weights of 350-1000g. No time increments given |
| A180 | DiMarco et al 1985 | Respiratory Muscle Endurance | | 11 | no gender | Muscular Dystrophy | RME assessed as max duration that ventilation levels of 30, 50, 70, and 90% of 15sMVV could be sustained. Test terminated after 15 min or bag no longer inflated. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Subjects</th>
<th>Exercise Intensity</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>A183</td>
<td>Respiratory Muscle Endurance</td>
<td>10 M</td>
<td>Elite cyclists</td>
<td>RME assessed by MSVC test = max ventilation sustainable for 10 min. Isocapnic hyperpnea. 2 min warm up at 50% max exercise ventilation. 1 rest, during first 2 min of test air flow increased from warm up level to max ventilation that could be sustained for 8 min. Repeated until 2 test 48 hrs apart were within 5%. Mean ventilation in last 8 minutes of highest test was baseline measurement.</td>
</tr>
<tr>
<td>A185</td>
<td>Respiratory Muscle Endurance</td>
<td>33 (13M)</td>
<td>25 = Rheumatoid Arthritis 21 = Control age and BMI matched</td>
<td>Not clear how RME was assessed either by MIP, MEP and MVV or just MVV by itself. No details on how MVV was measured, MIP and MEP only</td>
</tr>
<tr>
<td>A187</td>
<td>Respiratory Muscle Endurance</td>
<td>24 (18M)</td>
<td>Class III Heart Failure</td>
<td>RME determined by MSVC. Isocapnia maintained throughout. MSVC defined as highest breathing volume (L/min) that could be maintained for the entire 3 min.</td>
</tr>
<tr>
<td>A188</td>
<td>Respiratory Muscle Endurance</td>
<td>7 M</td>
<td>Experienced Climbers assessed between 3450 – 5350m</td>
<td>RME assessed by 1) 12 sec MVV 2) Maintenance of inspiratory load until fatigue develops modified Grassino 1991. Given a target of 50% MIP each subject inspired to target from RV and sustained this pressure for as long as possible. Time taken to task failure = Tlim sec</td>
</tr>
<tr>
<td>A190</td>
<td>RME Training</td>
<td>20 (7M)</td>
<td>Healthy</td>
<td>IME assessed by inspiratory threshold loading. Subjects inspired against a load = 10% Pimax and 25 g added every 1.5 min, pressure continually assessed. Breathing continued until inspiration could no longer be sustained. Pressure achieved during the heaviest load tolerated for at least 45 s was defined as maximal sustainable inspiratory pressure (SiPmax) Subjects divided into normocapnic and hypercapnic</td>
</tr>
<tr>
<td>A191</td>
<td>Respiratory Muscle Endurance</td>
<td>40 (20M)</td>
<td>CF 20 (10M) Controls (10M)</td>
<td>Subjects habituated to Sustained maximum inspiratory pressure (SMIP). 3 SMIPs, inspiratory target set at 80% of max pressure profile, subject matched target x6 over six consecutive levels with rest between each effort decreasing per level 1 min, 45 sec, 30 sec, 15 sec, 10 sec, 5 sec. Test halted when subject unable to match at least 90% of computer curve template/target.</td>
</tr>
<tr>
<td>A192</td>
<td>Respiratory Muscle Endurance</td>
<td>11 (M)</td>
<td>Triathletes 5 = elite 6 = competition</td>
<td>RME assessed by controlled breathing Matecki 2001. Tlim = max time subject can breathe against a predetermined inspiratory submax load = 75% of Pimax = Pm. IB = 15 min^{-1} and target of 700 ml VT at each inspiration. Test halted when subject could not maintain target volume for 3 breaths or when mouthpiece was rejected. Length of loaded breathing was defined as Tlim.</td>
</tr>
<tr>
<td>Reference</td>
<td>Title</td>
<td>Population</td>
<td>Method</td>
<td>Details</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td>Boussana et al 2003</td>
<td><strong>Respiratory Muscle Endurance</strong></td>
<td>10 (M)</td>
<td>Triathletes</td>
<td>RME assessed by controlled breathing. Matecki 2001. Tlim = max time subject can breathe against a predetermined inspiratory submax load = 75% of Pimax = Pm. IB = 15min⁻¹ and target of 700ml VT at each inspiration. Test halted when subject could not maintain target volume for 3 breaths or when mouthpiece was rejected. Length of loaded breathing was defined as Tlim.</td>
</tr>
<tr>
<td>Eastwood et al 2001</td>
<td><strong>Respiratory Muscle Endurance</strong></td>
<td>12 no gender</td>
<td>6 = endurance trained athletes 6 = sedentary controls</td>
<td>RME measured by ITL test (Martyn) Subjects breathed through a modified inspiratory threshold valve which required negative threshold pressure (Pth). No instructions given regarding fB. Pth was increased by adding weights and was monitored at the mouthpiece. Subjects sat quietly and breathed for 5 min through unloaded threshold valve while baseline metabolic and chest wall motion measurements were collected. Inspiratory load was then increased by 10% PImax measured at baseline every 2 min until the subject was no longer able to sustain the breathing task (task failure) Pth associated with each increase in load was recorded and expressed as a percentage of the subjects’ PImax (%PImax). RME expressed as max threshold pressure Pthmax. 4 tests &gt; 24 hrs apart</td>
</tr>
<tr>
<td>Sturdy et al 2004</td>
<td><strong>Respiratory Muscle Endurance</strong></td>
<td>10 (8M)</td>
<td>COPD</td>
<td>RME measured by ITL test (Martyn) Subjects breathed through a modified inspiratory threshold valve which required negative threshold pressure (Pth). No instructions given regarding fB. Pth was increased by adding weights and was monitored at the mouthpiece. Subjects sat quietly and breathed for 5 min through unloaded threshold valve while baseline metabolic and chest wall motion measurements were collected. Inspiratory load was then increased by 10% PImax measured at baseline every 2 min until the subject was no longer able to sustain the breathing task (task failure) Pth associated with each increase in load was recorded and expressed as a percentage of the subjects’ PImax (%PImax). RME expressed as max threshold pressure Pthmax. 4 tests &gt; 24 hrs apart</td>
</tr>
<tr>
<td>Tobin et al 2002</td>
<td><strong>Respiratory Muscle Endurance</strong></td>
<td>16 M</td>
<td>Duchenne Muscular Dystrophy</td>
<td>IME assessed by time limit (Tlim) = maximal time a subject able to sustain breathing against an inspiratory load without inspiratory muscle fatigue [Roussos 1979]. Patient could inhale against a resistance used as index of endurance. Children requested to breathe at constant inspiratory load =35% Pimax. Instruction given on fB. TV constant throughout and corresponded to the patient’s resting Vt. Loaded breathing continued until subject could no longer maintain target volume for 3 consecutive breaths or no longer tolerate the procedure. Period of loaded breathing was defined as the endurance time (Tlim).</td>
</tr>
</tbody>
</table>
| van der Esch et al | **Inspiratory Muscle Endurance** | 12 M | Ankylosing Spondylitis | IME assessed by 2 min incremental inspiratory threshold loading protocol (Martyns). End tidal CO2 monitored. 5 min unloaded breathing, then 25% Pimax applied, increased by 5% until subjects gave up. Subjects had to maintain VE at resting levels. Used loads }
<table>
<thead>
<tr>
<th>Year</th>
<th>Study Authors</th>
<th>Study Title</th>
<th>Gender</th>
<th>Age</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Weiner et al 1998</td>
<td>Respiratory Muscle Endurance</td>
<td>18 (8M)</td>
<td>Myasthenia Gravis</td>
<td>IME assessed by similar device to Nickerson &amp; Keens. Inspiratory elastic work increased by 25 – 100g weights every 2 min = Martyns, until exhaustion and subject no longer continue. Pressure achieved with heaviest load tolerated for at least 60 sec, defined as PmPeak.</td>
</tr>
<tr>
<td>2003</td>
<td>Saikikaya et al</td>
<td>Respiratory Muscle Endurance</td>
<td>51 (10M)</td>
<td>Obese &gt;BMI 25</td>
<td>No detail in method of Respiratory Muscle endurance assessment technique In Results = MVV measurement reflecting the respiratory muscle endurance (no detail in method of MVV)</td>
</tr>
<tr>
<td>2003</td>
<td>Cimen et al</td>
<td>Respiratory Muscle Endurance</td>
<td>142 F</td>
<td>Osteoporosis</td>
<td>No description of RME in either method or results In discussion = MVV values which reflect respiratory muscle endurance</td>
</tr>
<tr>
<td>2001</td>
<td>Covey et al</td>
<td>Respiratory Muscle Endurance</td>
<td>27 (18M)</td>
<td>COPD/Severe airflow obstruction FEV1&lt;50% pred or FEV1/FVC &lt;45% pred</td>
<td>RME assessed by discontinuous-incremental threshold loading protocol (DC-ITL). Adapted design of Nickerson &amp; Keens. Patients began at 30% of Pimax, increased every 2 min in 50g increments until symptom limited end point. Allowed 1 min rest between each 2 min stage. Peak load Pm defined as work load g of highest stage completed.</td>
</tr>
<tr>
<td>1990</td>
<td>Heimer et al</td>
<td>Respiratory Muscle Endurance</td>
<td>31 (18M)</td>
<td>Type 1 diabetes</td>
<td>MVV was measured using 12 second maximum voluntary ventilation test, and used as an index of RME</td>
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<tr>
<td>A226</td>
<td>Morgan et al 1987</td>
<td>Respiratory Muscle Endurance (RMET)</td>
<td>Ventilatory endurance</td>
<td>RMET</td>
<td>Endurance breathing time</td>
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<td></td>
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<td></td>
<td>9 M</td>
<td>Moderately trained cyclists</td>
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<td>Exp group = 4</td>
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<td>Control group = 5</td>
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<td></td>
<td>Endurance breathing test = time subjects could ventilate at 100% of 15 sec MV, re-breathed proportion of their expired CO2.</td>
<td></td>
</tr>
<tr>
<td>A227</td>
<td>O'Kroy et al 1993</td>
<td>Respiratory Muscle Endurance (RME)</td>
<td>Respiratory Muscle Performance (RMP)</td>
<td>RMT</td>
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<tr>
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<td></td>
<td>35 (16 M)</td>
<td>Untrained students</td>
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<td>Threshold loaded inspiratory fatigue bout (IF) assess 'RME in resistive strength mode' by threshold loaded valve similar to Nickerson &amp; Keens. At 80% MIP at freely chosen fB and TV, duty cycle maintained at 0.5 to prevent reduced inspiratory work. After each min, MIP reassessed and subject returned immediately to breathing through loaded valve, repeated until MIP fell to 80% of pre test MIP on 2 or more consecutive measurements, length time = time to fatigue.</td>
<td></td>
</tr>
<tr>
<td>A234</td>
<td>Walsh et al 1996</td>
<td>Respiratory Muscle Endurance (RME)</td>
<td>Inspiratory Muscle Endurance (IME)</td>
<td>IME</td>
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<td></td>
<td>30 (27) M</td>
<td>20 = stable chronic heart disease</td>
<td>10 (M) healthy age matched control</td>
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<td></td>
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<td>RME assessed by pressure threshold valve using a 2min incremental loading protocol (Martyn et al). Using a weighted plunger 100g, 100g added every 2 min until fatigue, not able to lift plunger over 2 consecutive breaths. Maximum tolerated threshold load that could he sustained for 2 mins = Pmax. Pmax also expressed as proportion of MIP provide measure of inspiratory load</td>
<td></td>
</tr>
</tbody>
</table>

**‘Inspiratory Muscle Endurance’**

<p>| | | | | | |</p>
<table>
<thead>
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</thead>
<tbody>
<tr>
<td>A124</td>
<td>Watsford et al 2007</td>
<td>Inspiratory Muscle Endurance (IME)</td>
<td>RM Function</td>
<td>IME</td>
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<td></td>
<td></td>
<td>72 (36M)</td>
<td>Healthy older adults A = 50-59yrs</td>
<td>B = 60-69</td>
</tr>
<tr>
<td></td>
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<td>IME assessed with POWERLUNG device. 2min incremental threshold loading test (Fiz et al). After inspiring against a resistance for 2min, 2min rest @ normal breathing, then threshold pressure increased, repeated until participant not overcome threshold pressure. Max pressure sustained for 2 min stage = Pend.</td>
<td></td>
</tr>
<tr>
<td>A136</td>
<td>Eastwood et al 1998</td>
<td>Inspiratory Muscle Endurance (IME)</td>
<td></td>
<td>IME</td>
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<td></td>
<td>18 (M)</td>
<td>Healthy control</td>
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<td>Progressive Inspiratory threshold loading (Martyn et al). Pth required to be developed with each inspiration could be increased by addition of weights to the valve. O2 uptake, CO2 output, Ve and component TV, fB, Ti, Te, Ttot and end-tidal CO2 tension were collected continuously. Protocol required subjects to sit quietly and breathe for 5 min through unloaded threshold valve for baseline, load increased by 100 g every 2 min until the subject was no longer able to sustain the breathing task. No instructions given regarding breathing Not stated but in results Pth Max = IME</td>
<td></td>
</tr>
<tr>
<td>A137</td>
<td>Clanton et al 1985</td>
<td>Inspiratory Muscle Endurance (IME)</td>
<td></td>
<td>IME</td>
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<td>6 (3M)</td>
<td>Healthy Normal’s</td>
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<td>Subjects breathed against threshold load (Nickerson &amp; Keens) with constant fB until not match 2/3rds of control target flow rate for at least 1/2 of control inspiratory phase for 3 consec breaths. Time from beginning to 1st breath subject could no longer match 2/3rds target flow used as measurement of endurance (Tlim).</td>
<td></td>
</tr>
<tr>
<td>A207</td>
<td>Johnson et al</td>
<td>Inspiratory Muscle Endurance (IME)</td>
<td>IMT</td>
<td>IMT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 no gender</td>
<td>Stable chronic heart failure</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Use THRESHOLD Trainer and pressure threshold valve (Eastwood &amp; Hillman). Subjects Inspired 4 min, total work calculated as pressure-time product (PTP)</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Authors</td>
<td>Study Title</td>
<td>End Expiration</td>
<td>Disease</td>
<td>IME Assessed Subjects</td>
</tr>
<tr>
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</tr>
<tr>
<td>1994</td>
<td>Wanke et al</td>
<td>Inspiratory Muscle Endurance</td>
<td>IMT</td>
<td>COPD</td>
<td>Nickerson &amp; Keens</td>
</tr>
<tr>
<td>1994</td>
<td>Foglio et al</td>
<td>Inspiratory Muscle Endurance Time</td>
<td>IMT</td>
<td>Multiple Sclerosis</td>
<td>Modified procedure (GROSS). Patients taught to breathe with a Pflex device set to elicit a mouth pressure of 70% MIP (target pressure) that had to be maintained. Expiration was unloaded and respiratory rate uncontrolled Endurance time was determined when patient was not able to sustain the target pressure for longer than three consec breaths,</td>
</tr>
<tr>
<td>1994</td>
<td>Mannix et al</td>
<td>Inspiratory Muscle Endurance</td>
<td>IMT</td>
<td>Healthy normal</td>
<td>Inspiratory muscle fatigue</td>
</tr>
<tr>
<td>1989</td>
<td>Chen et al</td>
<td>Inspiratory Muscle Endurance</td>
<td>IMT</td>
<td>Healthy Sedentary Chinese</td>
<td>Respiratory muscle function</td>
</tr>
<tr>
<td>1988</td>
<td>Dodd et al</td>
<td>Inspiratory Muscle Endurance</td>
<td>IMT</td>
<td>Normal</td>
<td>Respiratory Muscle Endurance</td>
</tr>
<tr>
<td>1995</td>
<td>Weiner et al</td>
<td>Inspiratory Muscle Endurance</td>
<td>IMT</td>
<td>Patients receiving corticosteroids for diseases other than respiratory conditions</td>
<td>Inspiratory Muscle Function</td>
</tr>
</tbody>
</table>

In results: Inspiratory muscle endurance as expressed by the relationship between PmPeak and the PIMax...
| A218 | Preuss et al 1994 | Inspiratory Muscle Endurance | IMT | 22 (8M) | Ambulatory COPD patients 
12=Group 1 High loading 
8=Group 2 low loading | 1). Symptom-limited pulmonary ITL test, subjects matched FB of 1 breath every 3 s, a duty cycle 0.33 and flow rate of 0.6 (L/s) for M subjects and 0.53L/s for F subjects. After breathing unloaded for 2 mm, threshold load began at -4 cm H2O and increased by -2 cm after every fifth breath (every15 s) until subject either signalled to stop test or unable to match FB , duty cycle, and flow rate during 3 of 5 breaths for that pressure load. Max threshold load successfully completed recorded as Pitl 
2) Inspiratory Endurance steady-state test = threshold load at 75% Pitl. Tlim determine point subject unable to match FB, duty cycle, and flow rate for 3 consec breaths. Load based on % of Pitl as this load more reproducible than load based on % of Pimax. Because improvement in IME a function of both increased endurance time and pressure, results reported in terms of the total external work performed during the IE test. Work (volume X average pressure XTlim)/3-s total breath period), where volume = average tidal volume per breath, expressed in liters. Pressure = average threshold pressure for each breath expressed in cm H2O, Tlim = total time of test in secs. Work is expressed in liters X cm H2O. |
| A220 | Weiner et al 1993 | Inspiratory Muscle performance | Inspiratory Muscle Endurance | 8 (4M) | Patients receiving corticosteroids for disease other than respiratory |
| A221 | Goldstein et al 1991 | Inspiratory Muscle Endurance | 6 (1M) | Patients with Respiratory Failure as a consequence of restrictive Ventilatory disease |
| A222 | Goldstein et al 1989 | Inspiratory Muscle Endurance | IMT | 5 no gender | IME measured by pressure threshold loading (Nickerson&Keens) = endurance time (Tlim) during which subject could maintain inspiration at 45% MIP. Subjects inspired against a weighted plunger sustaining throughout inspiration.: (1) duty cycle (TIF,F,ı) at 0.5; (2) FB resting level (3) VT at 125% of previously measured resting value, When subjects failed either to match preset ventilatory controls or to generate required pressure, they came off mouthpiece, effectively terminating test.

<p>| A223 | O'Donnell et al 1998 | Inspiratory Muscle Endurance | 20 (12M) | Chronic airflow limitation | IME assessed at load = approx 50% of max achieved in pre-control visit using threshold breathing device (Nickerson &amp;Keens) load remained constant for all tests: to a symptom-limited endpoint (Vlim). |</p>
<table>
<thead>
<tr>
<th>ID</th>
<th>Authors</th>
<th>Title</th>
<th>Methodology</th>
<th>Participants</th>
<th>IME measured</th>
</tr>
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<tbody>
<tr>
<td>A225</td>
<td>Inbar et al 2000</td>
<td>Inspiratory Muscle Endurance</td>
<td>IMT</td>
<td>20 no gender</td>
<td>Well trained endurance athletes</td>
</tr>
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<td></td>
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<td>10=IMT</td>
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<td>10-Control</td>
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<td>IME assessed with ITL device (Nickerson &amp; Keens), inspiratory elastic work increased by progressive addition of 25-100-g weights at 2-min intervals (Martyn) until subjects were exhausted and could no longer inspire. Pressure achieved with heaviest load (tolerated for at least 60 s) defined as peak pressure (PmPeak).</td>
</tr>
<tr>
<td>A231</td>
<td>De Jong et al 2001</td>
<td>Inspiratory Muscle Endurance</td>
<td>IMT</td>
<td>16 (8M) Cystic Fibrosis</td>
<td></td>
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<td></td>
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<td>8=IMT</td>
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<td>8=SHAM IMT</td>
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<td>IME assessed with threshold-loading device during an incremental loading procedure. Patients started inspirng at 30% Pimax for 2 min. Threshold load was increased every 2 min in increments 10% Pimax. Max load defined as highest load reached and maintained for at least 1 min as a % of Pimax. IB not regulated.</td>
</tr>
<tr>
<td>A232</td>
<td>Sette et al 1997</td>
<td>Inspiratory Muscle Endurance</td>
<td>RME assessed using technique (Nava)Children started breathed through inspiratory resistance 70% PImax as long as they could. FB 20 bpm, using metronome. Tl/Ttot and tidal volume measurements were obtained during unobstructed breathing. IME expressed as time from start of resistive run to moment when the patient could not maintain the target pressure for at least 5 consec breaths = &quot;limiting time&quot; (Tlim)</td>
<td>20 (17M) Bronchial Asthma 2 attempts</td>
<td></td>
</tr>
<tr>
<td>A236</td>
<td>Reiter et al 2006</td>
<td>Inspiratory Muscle Endurance</td>
<td>IME expressed as Tlim, defined as max time sustained breathing against a resistance and flow dependent load. Inspiratory resistance was variably adjusted. Subjects had to achieve 80% Plimax with each inspiratory maneuver, expiration unloaded. Visual feedback of inspiratory and expiratory pressures. FB at 15bpm paced by audio cassette. Time elapsed from start of test until exhaustion, when subject did not achieve 80% Plimax on 4 consec breaths was recorded (sec).</td>
<td>68 (29M) Healthy Normal's</td>
<td></td>
</tr>
<tr>
<td>A237</td>
<td>Inzelberg et al 2005</td>
<td>Inspiratory Muscle Endurance</td>
<td>IME assessed by inspirng through Nickerson &amp; Keens device. Inspiratory elastic work was increased by progressive addition of 25-100-g weights at 2-min intervals (Martyn) until subjects were exhausted and could no longer inspire. The pressure achieved with heaviest load (tolerated for at least 60 s) was defined as the peak pressure (PmPeak)</td>
<td>20 (12M) Parkinson's Disease</td>
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<td>10=IMT</td>
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<td></td>
<td>10=placebo (low load)</td>
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<tr>
<td>A238</td>
<td>Brancelone et al 2004</td>
<td>Inspiratory Muscle Endurance</td>
<td>IME assessed by ITL test, subjects started at 20% Plimax, increased at 2 min intervals by 10% Plimax. Mouth pressure, O2 sats and end tidal CO2 continuously measured. IME defined as max insp pressure tolerated for 2min (Plim2) and as % Plimax (Plim2/Plimax)</td>
<td>63 (33M) Sarcoidosis 19 = Healthy Controls</td>
<td></td>
</tr>
<tr>
<td>A239</td>
<td>Klefbeck et al 2000</td>
<td>Inspiratory Muscle Endurance</td>
<td>IME assessed with THRESHOLD inspiratory trainer, produces inspiratory pressure loads independent of flow. Patients breathed through device for 5 min and pointed end every min at RPE scale. Resistance (Pressure) was chosen through 2 to 3 sets with rest intervals between so that patients at end of the 5 min period rated 15 &quot;Hard&quot;. After 10-15 min rest resistance increased so that at end of the 5 min period patients rated 17 &quot;Very hard&quot;. The resistance (pressure) at 15 and 17 RPE was used as endurance value.</td>
<td>10 (7M) Polo</td>
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<td>7=IMT</td>
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<td>3=control</td>
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</tr>
<tr>
<td>A240</td>
<td>Scardella et al 1993</td>
<td>Inspiratory Muscle Endurance</td>
<td>5 M</td>
<td>Normal</td>
<td>IME assessed by repeating a sequence of 3 sec contractions followed by 4 sec relaxation (duty cycle 0.43) at 80% MIP until fatigue. Point subject failed to attain at least 90% previous generated inspiratory forced defined mechanical fatigue of inspiratory muscles. Expressed as Tlim in results</td>
</tr>
<tr>
<td>A242</td>
<td>Wanke et al 1991</td>
<td>Inspiratory Muscle Endurance</td>
<td>76 (61M)</td>
<td>Dependent diabetics</td>
<td>Parameter for endurance was 12sec MVV test (L/min) completed over 2 days, best two values recorded</td>
</tr>
<tr>
<td>A264</td>
<td>Ker et al 1996</td>
<td>Inspiratory Muscle Endurance</td>
<td>27 (15M)</td>
<td>COPD pFEV1 &lt;80%</td>
<td>RME defined as max load that subjects could maintain for 2 min interval against increasing ITL, expressed in gram weight = g, peak mouth pressure = Pmpk and relative load Pmpk/PImax. Modified Nickerson &amp; Keens device used, breathing patterns, mouth pressure, insp airflow and TV monitored continuously. IPM Integrated Mouth Pressure</td>
</tr>
<tr>
<td>A245</td>
<td>Collet et al 2007</td>
<td>Inspiratory Muscle Endurance</td>
<td>55 (12M)</td>
<td>Severe Obesity BMI &gt;35 kg/m2</td>
<td>IME assessed by ITL Test (Martyn). Subjects started at 20% Pimax, increased at 2 min intervals by 10% Pimax. Mouth pressure, O2 sats and end tidal CO2 continuously measured. IME defined as max insp pressure tolerated for 2min (Plim2) and as % PImax (Plim2/PImax). Low IME defined as Plim2/PImax &lt;60%</td>
</tr>
<tr>
<td>A246</td>
<td>Chen et al 1989P</td>
<td>Inspiratory Muscle Endurance</td>
<td>30 M</td>
<td>Healthy (sleep loss)</td>
<td>IME assessed by time against inspiratory pressure load (Nickerson &amp; Keen) at 60% Pimax at FRC, if sustained &gt;15 min, then load &gt;10% and repeated. Visual feedback of target and mouth pressure to guide each inspiration. Duty cycle (0.4) and IB (at rest level) were maintained through test. Test halted when target pressure missed 3 consec breaths. Pressure time index PTI (target pressure x endurance time) index of IME. CO2 and O2 continuously monitored.</td>
</tr>
<tr>
<td>A247</td>
<td>Chen H-I et al 1985</td>
<td>Inspiratory Muscle Endurance</td>
<td>13 (7M)</td>
<td>Stable COPD (pulmonary rehab)</td>
<td>1) IME measured pressure threshold test (Nickerson &amp; Keens) set at 60% Pimax at FRC. Subjects inspired until exhaustion time taken recorded. 2) SIP, highest % of Pimax generate for 10min determined by 10% decrement or increments in Pimax until subject could tolerate load for 10min, 15 min rest in between trials. FB and duty cycle unconstrained.</td>
</tr>
<tr>
<td>A248</td>
<td>Chen et al 1989C</td>
<td>Inspiratory Muscle Endurance</td>
<td>20 F</td>
<td>Healthy Sedentary</td>
<td>IME assessed by time against inspiratory pressure load (Nickerson &amp; Keen) at 60% Pimax at FRC. If sustained &gt;15 min, then load &gt;10% and repeated. Visual feedback of target and mouth pressure to guide each inspiration. Duty cycle (0.4) and IB (at rest level) were maintained through test. Test halted when target pressure missed 3 consec breaths. Pressure time index PTI (target pressure x endurance time) index of IME. CO2 and O2 continuously monitored.</td>
</tr>
<tr>
<td>A250</td>
<td>Newell et al 1989</td>
<td>Inspiratory Muscle Endurance</td>
<td>22 M</td>
<td>Chronic airflow obstruction</td>
<td>Subjects performed 10 maximal static contractions lasting 10 sec (5 sec rest between), at FRC in body plethysmography. Average pressure sustained, initial peak pressure and initial lung volume recorded. IME calculated as ratio between force in best of last two contractions and force in best of first 3 contractions. Expressed as %. Supplemental O2 at 6 L/min.</td>
</tr>
<tr>
<td>A261</td>
<td>McKeon et al 1986</td>
<td>Inspiratory Muscle Endurance</td>
<td>IMT</td>
<td>18 No gender</td>
<td>Chronic Airflow Limitation, during pulmonary rehab.</td>
</tr>
<tr>
<td>A262</td>
<td>Innes et al 1982</td>
<td>Inspiratory Muscle Endurance</td>
<td>IMT</td>
<td>11 (7M)</td>
<td>CF</td>
</tr>
<tr>
<td>A264</td>
<td>Ker et al 1996</td>
<td>Inspiratory Muscle Endurance</td>
<td>Endurance def' by length time load can be endured before process of fatigue develops sufficiently to cause task failure</td>
<td>10 (6M)</td>
<td>Ultra-Marathon Runners (Above average)</td>
</tr>
</tbody>
</table>

### ‘Ventilatory Muscle Endurance’

<p>| A114 | Nickerson et al 1982 | Ventilatory Muscle Endurance | Endurance is the property that affords resistance to fatigue | 15 (4M) | Healthy Normal | Inspiratory pressure threshold (Pth) load via weighted plunger, at sustained inspiratory pressure. Begin inspiring at Pth near MIP until fatigue, rest at least 10x duration of that run. Repeated after decreasing weight by 5% until subject can inspire against Pth for 10 min. This pressure = SIP = average mouth pressure of last 20 breaths as SIP. fB and duty cycle unconstrained. |
| A252 | Levine et al 1992 | Ventilatory Muscle Endurance | | 5 M | COPD receiving 4hr/day NPV | VME assessed as MSVC for 12 min. Incremental target flow rate (resting ventilation) increased incrementally to determine max ventilation subject could maintain for 12 min. Insp min ventilation during highest target flow rate termed MSVC. Continually measured end tidal CO2 and O2 sats. |
| A254 | Keenan et al 1995 | Ventilatory Muscle Endurance | | 27 (14M) | 13 = Generalised Myasthenia gravis 13 = Ocular Myasthenia gravis 10 = normal’s | VME assessed by 2min incremental threshold loading test, weighted plunger. Subjects began with 50g load increased every 2 min until not continue. Last load completed for 2 min = max load (g) and mean mouth pressure over 6 breaths at max load = P(average) were taken as measures of RME |
| A255 | Belman et al 1988 | Ventilatory Muscle Endurance | VMT | 25 (11M) Elderly (65-75yr) Healthy VMT = 12 (7M) Control = 13 (4M) | VME assessed by MSVC. 1st “practice” MSVC measured at flow rate 70% previously measured MVV and adjusting flow rate during first 2 min. Subsequent MSVC tests flow rate initially set at slightly above previously recorded MSVC. Adjustments in flow were made to encourage maximal effort. Average MSVC value was calculated using the last 8 min of the 10-min test. |
| A256 | Martin et al 1982a | Ventilatory Muscle Endurance | 9 (4M) Active healthy | No direct measurement of VME Work designed to reduce VME consisted of 150 min of sustained max ventilation performed isocapnically – Long term hypernea regimen – subjects asked to maintain max possible ventilation 150 min period. FB at or &lt;60bpm by metronome. Every 15 min subjects had 4 min rest. Ve and Vo measured continually. Decrease in VME indicated by decrease in Ve and Vo as hypernea test progressed |
| A257 | Ries et al 1986 | Ventilatory Muscle Endurance | 12 (3M) COPD pulmonary rehab | No defined measurement of VME MVV, MSVC used to assess ventilatory muscle performance |
| A258 | Belman et al 1982a | Ventilatory Muscle Endurance | Physical Training | 15 No Gender COPD | VME assessed by MSVC defined as max minute ventilation sustained for 15 min under isocapnic conditions. Test repeated x2, test with highest MSVC was used for later comparison. |
| A259 | Silva et al 1998 | Ventilatory Muscle Endurance | Aerobic Training | 24 M 12 = Spinal Cord Injury 12 = matched controls | VME assessed sustained time at 70% MVV-12sec value (70%-MVV time). Hypocapnia avoided by partial rebreathing. Expired FE CO2 maintained range (5±1%). IB and B pattern uncontrolled. Test ended when subject unable to sustain target ventilation, with reduction higher than 10%. |
| A260 | Bradley et al 1976 | Ventilatory Muscle Endurance | | | Sustainable Ventilatory Capacity used as index of VME. |
| A266 | Inselman et al 1993 | Ventilatory Muscle Endurance | 13 (8M) Obese children 147 – 300% Ideal body weight | VME not referred to in methods or results, in discussion measurement of MVV indicates ventilatory capacity and ventilatory muscle endurance. No detail of MVV assessment. |
| A267 | Loveridge et al 1989 | Ventilatory Muscle Endurance | VMT | 12 No Gender Quadruplegics 6 = VMT 6 = control | Sustainable Inspiratory Pressure used as index of VME, assessed by modified Nickerson &amp; Keens threshold load device at 75% MIP until exhaustion. If &gt;10 min, 2nd test at 85% MIP, if &lt;10min 2nd test at 65% MIP Pressure time plot made between 2 points, extrapolated pressure at 10 min = SIP |
| A268 | Warren et al 1989 | Ventilatory Muscle Endurance | | 10 (9M) Ultra-marathon runners | VME assessed by 12-MVV (stated in intro and results not method) to ATS standards except only made x2 not x3 due to time. |
| A269 | Ries et al 1988 | Ventilatory Muscle Endurance | Upper extremity training | 28 No gender COPD pulmonary rehab | VME assessed by tidal breathing through inspiratory resistive device PFLEX to determine smallest orifice patients could sustain for 10min, 10 min rest between trials. Smallest orifice sustained for 10 min and time next smallest orifice recorded. |</p>
<table>
<thead>
<tr>
<th>A270</th>
<th>Levine et al 1986</th>
<th>Ventilatory Muscle Endurance</th>
<th>VMET</th>
<th>32 M</th>
<th>COPD Patients matched pairs 15 = VMET 17 = IPPB(placebo)</th>
<th>No mention of VME in method or results, in introduction describes other papers using MSVC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A271</td>
<td>Martin et al 1986</td>
<td>Respiratory Muscle Endurance</td>
<td>RMT</td>
<td>18 M</td>
<td>Duchenne Muscular Dystrophy</td>
<td>No definition of RME or VME in method or results. In discussion states that RME/VME = time Pimax and Pemax could be held for. Max time each max static insp and exp pressure could be held was recorded until reading fell below 90 Pi and Pe max.</td>
</tr>
<tr>
<td>A273</td>
<td>Belman et al 1980</td>
<td>Ventilatory Muscle Performance</td>
<td>VMT</td>
<td>10</td>
<td>COPD</td>
<td>No description of VMP/VME assessment in methods or results. Probably used MSVC as index?</td>
</tr>
<tr>
<td>A274</td>
<td>Forte et al 1997</td>
<td>Ventilatory Muscle Endurance</td>
<td>Endurance of the Inspiratory muscles can be measured as the capacity to sustain intense breathing tasks</td>
<td>18 M</td>
<td>Healthy</td>
<td>VME = no definition in methods or results. In Discussion defined as MSV</td>
</tr>
</tbody>
</table>

**Breathing Endurance**

<p>| A46  | Peret et al 2000 | Breathing Endurance | 20 M | Healthy 10 = Exp 10 = Con | BE assessed by: 1) Incremental breathing test, against Inspiratory resistive load at 60% Pimax for at least 3min. Expiration unloaded, IB 18bpm paced by metronome. Every 3 min load increased by 5% Pimax, until subjects no longer able to continue. Last step sustained for 3 min = target pressure for constant load test. 2) Constant load breathing test a target pressure (above) until task failure. IB 18bpm. Max breathing endurance time = start to task failure |
| A59  | Kohl et al 1997 | Breathing Endurance | RMT | 8 (6M) | Healthy | BE assessed by time at 70% MVV until exhaustion |</p>
<table>
<thead>
<tr>
<th>Study Code</th>
<th>Authors</th>
<th>Endurance Type</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Notes</th>
</tr>
</thead>
</table>
| A26        | Markov et al 1996 | Breathing Endurance | RMT | 16 (8M) | Healthy Active  
8 = RMT  
8 = Control  
BE assessed by training device, instructed to breathe at individually determined frequency and tidal volume until exhaustion, TV targeted at 60% VC and FB calculated to obtain VE approx 70% MVV. **Time to exhaustion = BE** |
| A52        | Boutellier et al 1992 | Breathing Endurance | RMT | 8 | Normal endurance trained  
BE assessed by voluntarily breathing with individually adjusted FB and TV, both chosen so that exhaustion occurred <10min. Time recorded when subject no longer maintain FB or TV. |
| A60        | Boutellier et al 1992 | Breathing Endurance | RMT | 4 (3M) | Healthy Sedentary  
BE assessed by subjects breathing at FB 45bpm and a TV of 2.5-3.0 L (60-66% VC), when subjects could maintain target time recorded. |
| A275       | Williams et al 2002 | Breathing Endurance | RMT | 7 (5M) | Healthy Runners  
Breathing endurance capacity assessed with inspiratory resistive device set at 60% MIP. Duty cycle 0.5, FB 22bpm. After each minute MIP taken, subject returning to loaded breathing. Procedure continued until two conec MIPs ≤80% of pre-fatigue MIP, time = BET |
| A276       | Martin et al 1982 | Ventilatory Endurance | IMT | 16 (8 M) | Healthy  
8 = athletes  
8 = siblings  
VE assessed by 1) 12 sec MVV 2) 80% MVV until exhaustion |

**Journal Search**

<table>
<thead>
<tr>
<th>Study Code</th>
<th>Authors</th>
<th>Endurance Type</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Notes</th>
</tr>
</thead>
</table>
| A278       | Hill et al 2007 | Inspiratory Muscle Endurance | IMT | 33 (22M) | COPD  
16 IMT  
17 placebo  
1) Incremental test – modified threshold loading valve, subject chose breathing pattern. Insp loads increased by 10% of baseline MIP until task failure. IME defined as Pthmax (max pressure) sustained for a minimum of 30 sec.  
2)Constant load test – breath against load determined during familiarization stage to elicit Tlim 5-10min ~80 baseline Pth.max. IME defined as Tlim. |
| A279       | Jardim et al 2007 | Endurance of Respiratory Muscle Function | IMT | 13 | Healthy post grad students  
RME measured with aneroid manovacuometer, subject inspiring generating pressure corresponding to 80% MIP in each respiratory Cycle. Max time (sec) tolerated at 20% considered endurance measurement. |
## Appendix 2.1 Continued

### 'Respiratory Muscle Endurance'

<table>
<thead>
<tr>
<th>Author</th>
<th>Result</th>
<th>Study Design</th>
<th>Technique</th>
<th>References; Nickerson &amp; Keens, Martyn, Leith and Bradley</th>
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</thead>
<tbody>
<tr>
<td>Scherer et al 2000</td>
<td>1. RMT 320.3±48.6 Control 400.2±68.0 (seconds)</td>
<td>cohort</td>
<td>Threshold Loading</td>
<td>NK</td>
</tr>
<tr>
<td></td>
<td>2. RMT 106±26.6 Control 117.8±22.7 (grams)</td>
<td></td>
<td>MVV A &amp; B</td>
<td></td>
</tr>
<tr>
<td>Stuessi et al 2001</td>
<td>Breathing Endurance (mins) RMT group 5.2 (sd 2.9) Control 6.5 (sd 5.7)</td>
<td>cohort</td>
<td>MVV A</td>
<td></td>
</tr>
<tr>
<td>Mueller et al 2006</td>
<td>RET min Paraplegia Tetraplegia</td>
<td>Cohort</td>
<td>MVV A</td>
<td>LB</td>
</tr>
<tr>
<td></td>
<td>20% = 51.8 20% = 46.0 40% = 38.8 40% = 19.9 60% = 12.2 50% = 4.2</td>
<td></td>
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<tr>
<td>Fiz et al 1998</td>
<td>Cmax, g</td>
<td>cohort</td>
<td>Threshold Loading</td>
<td>NK, M</td>
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<td></td>
<td>male female</td>
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<tr>
<td></td>
<td>1. 640.0±195.5 580.0±204.4</td>
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<td>B C1</td>
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<td>2. 570.0±170.3 327.3±110.4</td>
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<td>3. 440.0±117.3 333.3±70.7</td>
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<td>4. 310.0±73.8 288.9±105.4</td>
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<td>5. 220.0±91.9 310.0±152.4</td>
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<td>male female</td>
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<td></td>
<td>1. 701.2±228.8 650.0±267.3</td>
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<td>2. 565.8±185.9 412.2±196.2</td>
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<td>3. 470.6±104.5 386.2±146.5</td>
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<td>4. 344.0±71.5 374.3±121.6</td>
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<tr>
<td></td>
<td>5. 316.6±79.2 297.3±56.5</td>
<td></td>
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</tr>
<tr>
<td>Number</td>
<td>Author(s)</td>
<td>Year</td>
<td>Methodology</td>
<td>Results</td>
</tr>
<tr>
<td>--------</td>
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<td>-------------------------------------------------------------------------</td>
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<tr>
<td>A132</td>
<td>Larson et al.</td>
<td>1999</td>
<td>Calculated mean of 3 tests</td>
<td>Duration: Men = 18.3 min, Women = 20.1 min</td>
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<tr>
<td></td>
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<td></td>
<td>Rel mouth pr: Men = 59.7% of P&lt;sub&gt;Imax&lt;/sub&gt;, Women = 64.7% of P&lt;sub&gt;Imax&lt;/sub&gt;</td>
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<tr>
<td></td>
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<td></td>
<td>Ab mouth pr: Men = 43.7 cm H&lt;sub&gt;2&lt;/sub&gt;O, Women = 42.0 cm H&lt;sub&gt;2&lt;/sub&gt;O</td>
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<tr>
<td></td>
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<td>ITL weight: Men = 337.3 g, Women = 323 g</td>
</tr>
<tr>
<td>A138</td>
<td>McElvaney et al.</td>
<td>1989</td>
<td>Calculated average of 3 tests</td>
<td>Duration: Men = 20.1 min, Women = 20.1 min</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>Rel mouth pr: Men = 64.7% of P&lt;sub&gt;Imax&lt;/sub&gt;, Women = 64.7% of P&lt;sub&gt;Imax&lt;/sub&gt;</td>
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<td></td>
<td>Ab mouth pr: Men = 42.0 cm H&lt;sub&gt;2&lt;/sub&gt;O, Women = 42.0 cm H&lt;sub&gt;2&lt;/sub&gt;O</td>
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<td>ITL weight: Men = 323 g, Women = 323 g</td>
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<tr>
<td>A152</td>
<td>Koppers et al.</td>
<td>2006&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1) P&lt;sub&gt;Imax&lt;/sub&gt;</td>
<td>1) Max load = 636.7 g</td>
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<td></td>
<td>2) Tlim = 6.36 min</td>
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<td>RMET = 25 (sd 09) cmH&lt;sub&gt;2&lt;/sub&gt;O</td>
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<td>Control = 29 (sd12) cmH&lt;sub&gt;2&lt;/sub&gt;O</td>
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<td>2) HET</td>
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<td></td>
<td>RMET = 534 (sd 349) s</td>
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<td>Control = 389 (sd 265) s</td>
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<td></td>
<td><em>Randomly assigned to groups</em> no explanation of differences of baseline scores</td>
</tr>
<tr>
<td>A153</td>
<td>Mador et al.</td>
<td>2005</td>
<td>1) RM Time, min</td>
<td>RMT = 13.2±1.7 Control = 10.6±1.6</td>
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<td>2) VE, %MVV RMT 69.1±1.8 Control 69.9±2.6</td>
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<tr>
<td>A154</td>
<td>Wirnsberger et al.</td>
<td>1997</td>
<td>Patient 756 sec (sd 246) Control 869 sec (sd 130)</td>
<td>Matched healthy control</td>
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<td>Tlim = 8.4±0.9 min at 55.0±2.8% MVV Viim = 555±87 L</td>
</tr>
<tr>
<td>A156</td>
<td>Rassler et al.</td>
<td>2007</td>
<td>Tlim = 8.4±0.9 min</td>
<td>Control &gt;30 min (stopped testing)</td>
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<td>Tlim = 8.4±0.9 min at 55.0±2.8% MVV Viim = 555±87 L</td>
</tr>
<tr>
<td>A157</td>
<td>Malecki et al.</td>
<td>2001</td>
<td>Tlim DMD = 4.47 min</td>
<td>Matched healthy control</td>
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<tr>
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<td></td>
<td>Tlim DMD = 4.47 min at 55.0±2.8% MVV Viim = 555±87 L</td>
</tr>
</tbody>
</table>

<sup>a</sup> Calculated average of 3 tests.

<sup>b</sup> Matched healthy control.
<table>
<thead>
<tr>
<th>Paper ID</th>
<th>Authors</th>
<th>Year</th>
<th>Study Details</th>
<th>Cohort</th>
<th>Threshold Loading</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A160</td>
<td>Koechlin et al 2005</td>
<td>2005</td>
<td>Time Pre Puberty 138.5 sec (s.d) 20.9 Near end puberty = except 1 subject all able to continue for than 1,200 sec (20min) tests halted.</td>
<td>Cohort</td>
<td>Threshold loading C2</td>
<td>NK</td>
</tr>
<tr>
<td>A161</td>
<td>Laghi et al 2005</td>
<td>2005</td>
<td>Time of total loaded breathing Hypo = 302 sec ±29 Euo = 313 sec±48</td>
<td>Cohort</td>
<td>Threshold loading B</td>
<td>NK, M</td>
</tr>
<tr>
<td>A162</td>
<td>Chang et al 2005</td>
<td>2005</td>
<td>FRI = 0.88% (sd 0.13)</td>
<td>Cohort</td>
<td>Threshold loading C2</td>
<td></td>
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<tr>
<td>A163</td>
<td>Koessler et al 2001</td>
<td>2001</td>
<td>Baseline 12sMVV (L/min) A = 52.23 ±27.8 B = 56.9 ±24.75 C = 61.2 ±14.2</td>
<td>Cohort</td>
<td>MVV</td>
<td>LB</td>
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<tr>
<td>A164</td>
<td>Weiner et al 1992</td>
<td>1992</td>
<td>RME RMT group = 67.5 ±3.1 Control group = 66.7±2.0</td>
<td>Cohort</td>
<td>Threshold loading B</td>
<td>NK, M</td>
</tr>
<tr>
<td>A165</td>
<td>Nava et al 1992</td>
<td>1992</td>
<td>Endurance time Group A = 234.8± 48.9 Group B = 187.2 ±31.06</td>
<td>Cohort</td>
<td>Fixed Resistance tube</td>
<td></td>
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<tr>
<td>A166</td>
<td>Lake et al 1990</td>
<td>1990</td>
<td>1) Progressive Control 782 sec ±258 A 695 secs±328 B 538 secs±236 C 542 secs±208 2) Endurance control 224sec ±163 A 189±194 B 140±72 C 135±78</td>
<td>Cohort</td>
<td>Threshold loading B + C1</td>
<td>NK, M</td>
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<tr>
<td>A167</td>
<td>Morrison et al 1989</td>
<td>1989</td>
<td>There was no significant difference between tests with unfixed or fixed breathing frequency for any of the measures of RM endurance (max load, Ppk, Ppk/MIP, Pmean). Data in figs only not tabulated or given in result section</td>
<td>Cohort</td>
<td>Threshold loading B</td>
<td>NK, M</td>
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<tr>
<td>A168</td>
<td>Morrison et al 1989</td>
<td>1989</td>
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<td>Matched healthy control</td>
<td>Threshold Loading B</td>
<td>NK, M</td>
</tr>
<tr>
<td>A171</td>
<td>Sonne et al 1982</td>
<td>Not given in body of results. 0.48 cm ±0.03</td>
<td>cohort</td>
<td>Fixed Orifice C2</td>
<td></td>
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<tr>
<td>A172</td>
<td>Orenstein et al 1981</td>
<td>SH score Exercise group = 713.6 units (sd 390.5) Control group = 943.2 units (sd 254.2)</td>
<td>Unmatched healthy control</td>
<td>MSVC C1 LB</td>
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<tr>
<td>A173</td>
<td>Holm et al 2004</td>
<td>Not given in data or body of text fig only Endurance capacity of the respiratory muscles (estimated as sustainable ventilatory capacity) no data</td>
<td>cohort</td>
<td>MSVC C2 LB</td>
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<tr>
<td>A174</td>
<td>Boussana et al 2001</td>
<td>Tlim basline (not given in body of text fig and abstract only) Trial 1 = 4.19 min ±0.3 Trial 2 = 4.02 min ±0.3</td>
<td>cohort</td>
<td>Threshold loading B NK</td>
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<tr>
<td>A175</td>
<td>Weiner et al 1998a</td>
<td>IME ratio PmPeak/Pimax = 56 (SE1.4) %</td>
<td>Cohort</td>
<td>Threshold loading B NK, M</td>
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<tr>
<td>A176</td>
<td>Uijl et al 1999</td>
<td>Baseline Pendu = 3.98 Kpa</td>
<td>Cohort</td>
<td>Threshold loading B M, LB</td>
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<tr>
<td>A177</td>
<td>Chatham et al 1996</td>
<td>No data in body or abstract, fig only.</td>
<td>Pilot cohort</td>
<td>Fixed Orifice C1 NK</td>
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<tr>
<td>A178</td>
<td>Mancini et al 1995</td>
<td>MSCV L/min RMT 70 ±21 Control 49 ±11</td>
<td>cohort</td>
<td>MSVC B LB</td>
<td></td>
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<tr>
<td>A179</td>
<td>Supinski et al 1985</td>
<td>Placebo 79% MIP 397±107 89% MIP 110±21 Caffeine 79% MIP 856±142 90% MIP 272±47</td>
<td>cohort</td>
<td>Threshold loading B NK</td>
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<tr>
<td>A180</td>
<td>DiMarco et al 1985</td>
<td>Given as 100% from which intervention was measured. No individual data except In a fig.</td>
<td>cohort</td>
<td>MVV A LB</td>
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<tr>
<td>A183</td>
<td>Fairban et al 1991</td>
<td>MSVC</td>
<td>RMT group = 155.4±11.2 L/min</td>
<td>Control group = 155.1±26 L/min</td>
<td>cohort</td>
<td>MSVC</td>
</tr>
<tr>
<td>A185</td>
<td>Cimen et al 2002</td>
<td>MVV(%)</td>
<td>Patients = 85.80±17.80</td>
<td>Control = 96.19±15.67</td>
<td>Matched healthy control</td>
<td>MVV</td>
</tr>
<tr>
<td>A187</td>
<td>McConnell et al 2003</td>
<td>MSVC = 45.0 (sd 11.0)</td>
<td>cohort</td>
<td>MSVC</td>
<td>C2</td>
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</tr>
<tr>
<td>A188</td>
<td>Sharma et al 2007</td>
<td>MVV @ 3450 m = 166±24.71</td>
<td>MVV @ 5350 m = 120.14±24.48</td>
<td>Tlim @ 3450 m = 14.27±4.43</td>
<td>Tlim @ 5350 m = 12.96±3.39</td>
<td>cohort</td>
</tr>
<tr>
<td>A190</td>
<td>Koppers et al 2006</td>
<td>Sipmax(kPa)</td>
<td>Normocapnic = 3.6 (sd 1.6)</td>
<td>Hypercapnic = 4.5 (sd 1.9)</td>
<td>cohort</td>
<td>Threshold loading</td>
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<tr>
<td>A191</td>
<td>Enright et al 2006</td>
<td>IWC (j breath−1)</td>
<td>CF = 9.7 (SD 2.8) Controls = 11.8 (SD 2.8)</td>
<td>Matched healthy control</td>
<td>Threshold loading</td>
<td>B</td>
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<tr>
<td>A192</td>
<td>Boussana et al 2002</td>
<td>No pre intervention Tlim data in abstract or body of text, fig only.</td>
<td>cohort</td>
<td>Threshold loading</td>
<td>C1</td>
<td>NK, M</td>
</tr>
<tr>
<td>A193</td>
<td>Boussana et al 2003</td>
<td>Tlim min 5.22±0.28</td>
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<td>Threshold loading</td>
<td>C1</td>
<td>NK</td>
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<tr>
<td>A194</td>
<td>Eastwood et al 2001</td>
<td>Pthmax as a proportion of their PImax (3rd test)</td>
<td>Sedentary = 78 ±10%</td>
<td>Athletes = 90 ±9%</td>
<td>Unmatched healthy controls</td>
<td>Threshold loading</td>
</tr>
<tr>
<td>A195</td>
<td>Sturdy et al 2004</td>
<td>Baseline test 1</td>
<td>Pthmax = 35 ±17 not clear whether Pthmax is expressed as % or cmH2O</td>
<td>cohort</td>
<td>Threshold loading</td>
<td>B</td>
</tr>
</tbody>
</table>

**Note:**
- Table continues with similar entries.
- The table details various studies with their respective measurements and comparisons.
| A196 | Tobin et al 2002 | Tlim @ baseline | Trained 307.6 ±126.6 sec | Control 271±40.4 sec | Double blind RCT (training study) | Threshold loading | NK, M |
| A198 | van der Esch et al 2004 | PIend not reduced on average (mean = 103±36% pred) | Cohort | Threshold loading | B | M |
| A199 | Weiner et al 1998 | RME - as expressed by relationship between PmPeak and Pimax (not defined in methods appears to be %). | Cohort | Threshold loading | B | NK, M, LB |
| A200 | Sairikaya et al 2003 | MVV % (of predicted values?) | Obese 97.92 ±20.00 | Control 98.75 ±15.56 | Unmatched healthy controls | MVV | A |
| A202 | Cimen et al 2003 | MVV % | Patient = 83.35 ±19.14 | Control = 74.74 ±21.77 | Matched healthy controls | MVV | A |
| A203 | Covey et al 2001 | Pm cmH2O | IMT group = 37 (SD 12) | Control group = 44 (SD15) | Single blind RCT (Training study) | Threshold loading | DC-ITL | NK |
| A205 | Heimer et al 1990 | MVV% pred | Diabetes = 88.9 ±20. | Control = 103.9 ±15.8 | Matched healthy controls | MVV | A |
| A226 | Morgan et al 1987 | EBT sec | MVV (l/min) | | Unmatched control | MVV | A | LB |
| A227 | O'Kroy et al 1993 | No data only figs. | cohort | Threshold Loading | CI | NK, LB |
| A234 | Walsh et al 1996 | Pmax (cmH2O) | Patients 18.5 (6.4) | Control 30.7 (6.6) | Matched Healthy Controls | Threshold loading | B | NK, M |
### Inspiratory Muscle Endurance

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
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<th>Cohort</th>
<th>Threshold Loading</th>
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<tr>
<td>Watsford et al 2007</td>
<td>Pend (cmH20)</td>
<td>Male: 88.0 ± 14.5, Female: 77.5 ±20.5</td>
<td>cohort</td>
<td>B</td>
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<td>Male: 80.5 ±19.5, Female: 52.0 ±18.1</td>
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<td>Male: 67.0 ±24.4, Female: 39.3 ±13.4</td>
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<td>Eastwood et al 1998</td>
<td>Pth Max (cmH20)</td>
<td>Male: 69 ±17</td>
<td>cohort</td>
<td>NK, M</td>
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<tr>
<td>Clanton et al 1985</td>
<td>Tlim (min) All subjects</td>
<td>153 ±52</td>
<td>cohort</td>
<td>NK</td>
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<tr>
<td>Johnson et al 1996</td>
<td>No data not clear work load patients inspired at. deals with comparison of devices rather than measure of IME.</td>
<td>cohort</td>
<td>Threshold loading C1</td>
<td>NK</td>
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<td>Wanke et al 1994</td>
<td>Tlim (min) Controls</td>
<td>12.0 ±6.7 IMT, 12.2 ±6.2</td>
<td>RCT (training study)</td>
<td>NK, LB</td>
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<tr>
<td>Foglio et al 1994</td>
<td>Endurance time (sec)</td>
<td>Group I (able to complete exercise test n=16): 397 ±1545 (SD error?)</td>
<td>cohort</td>
<td>Resistive Threshold C1</td>
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<td>Group II (not able to complete exercise test n=8): 247 ±148</td>
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<td>Mannix et al 1993</td>
<td>IME Time (min)</td>
<td>@21% O2: 3.3 ±0.4, @13% O2: 1.6 ±0.4, @30% O2: 4.0 ±0.6</td>
<td>cohort</td>
<td>Threshold loading C1</td>
</tr>
<tr>
<td>Chen et al 1989a</td>
<td>Endurance time (sec)</td>
<td>M = 396 ±29, F = 404 ±30</td>
<td>cohort</td>
<td>Threshold loading C1</td>
</tr>
<tr>
<td>Dodd et al 1988</td>
<td>Tlim (sec) @15bpm</td>
<td>504 ±76</td>
<td>cohort</td>
<td>Threshold loading C1</td>
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<tr>
<td></td>
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<td>@22bpm 297 ±31, @30bpm 164 ±12</td>
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<tr>
<td>A217</td>
<td>Weiner et al 1995</td>
<td>PmPeak/PImax</td>
<td>Group A</td>
<td>82.7 ±2.6%</td>
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<td>A218</td>
<td>Preusser et al 1994</td>
<td>Pitl cm H20</td>
<td>Group 1</td>
<td>14 ± 6</td>
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<tr>
<td>A220</td>
<td>Weiner et al 1993</td>
<td>PmPeak/PImax</td>
<td>84.4 ±2.4%</td>
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<tr>
<td>A221</td>
<td>Goldstein et al 1991</td>
<td>Tim min</td>
<td>7.1 ±3.4</td>
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<td>A222</td>
<td>Goldstein et al 1989</td>
<td>Tim min</td>
<td>4.90 ±1.31</td>
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<td>A223</td>
<td>O'Donnell et al 1998</td>
<td>VLm Reports the increase but not actual values in text, results in bar chart</td>
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<td>A225</td>
<td>Inbar et al 2000</td>
<td>PmPeak cm H20</td>
<td>IMT</td>
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<td>A231</td>
<td>De Jong et al 2001</td>
<td>IME (%PImax)</td>
<td>IMT = 50 (SD 5)</td>
<td>SHAM = 49 (SD 12)</td>
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<tr>
<td>A232</td>
<td>Sette et al 1997</td>
<td>Tim (sec)</td>
<td>1st. 154 ±65</td>
<td>2nd. 164 ±66</td>
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<td>A236 Reiter et al 2006</td>
<td>Tlim (sec) mean(sd)</td>
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<tr>
<td>Age</td>
<td>Women</td>
<td>Men</td>
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<td>17-29</td>
<td>902.4 (416.91)</td>
<td>842.33 (166.14)</td>
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<td>30-39</td>
<td>791.08 (315.48)</td>
<td>847.34 (384.34)</td>
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<td>40-49</td>
<td>834.79 (384.45)</td>
<td>878.61 (344.22)</td>
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<td>50-59</td>
<td>942.09 (221.00)</td>
<td>991.75 (193.87)</td>
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<tr>
<td>60-69</td>
<td>648.44 (179.48)</td>
<td>854.76 (253.66)</td>
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<td>Threshold loading</td>
<td>NK, M</td>
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<td>C1</td>
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<thead>
<tr>
<th>A237 Inzelberg et al 2005</th>
<th>PmPeak (cmH2O) IMT</th>
<th>Placebo Controlled (training study)</th>
<th>Threshold loading B</th>
<th>NK, M</th>
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<tbody>
<tr>
<td></td>
<td>20.0 ±2.8 Placebo 18.2 ±2.3</td>
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<thead>
<tr>
<th>A238 Brancelone et al 2004</th>
<th>Plim2 (cmH20) Plim2/Plmax (cmH2O)</th>
<th>Unmatched healthy controls</th>
<th>Threshold loading B</th>
<th>NK</th>
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<tr>
<td>Sarcoid</td>
<td>89 ±4 53 ±3</td>
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<tr>
<td>Control</td>
<td>103 ±5 75 ±2</td>
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<table>
<thead>
<tr>
<th>A239 Klefbeck et al 2000</th>
<th>Res @ 15 RPE Res @ 17 RPE 10.7 (5.0-16.5) 11.9 (6.0-18.0) cmH2O</th>
<th>Cohort</th>
<th>Threshold loading C1</th>
<th>NK, LB</th>
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<tbody>
<tr>
<td></td>
<td>Unclear whether baseline is n=10 or n=7</td>
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| A240 Scardella et al 1993     | No data in tables or results Fig only                             | Cohort               | Inspiratory Load C1 |       |

| A242 Wanke et al 1991         | MVV (L/min) Diabetic 153.2 ±35.1 Control 167.2 ±50.6               | Unmatched healthy controls | MVV A | LB |

<table>
<thead>
<tr>
<th>A244 Ker et al 1996</th>
<th>1st week test results used</th>
<th>cohort</th>
<th>Threshold loading B</th>
<th>NK, M</th>
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<tr>
<td>Max Load(g)</td>
<td>235 (sd 97.9)</td>
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<td>Pmpk (cm H2O)</td>
<td>34 (sd 11.4)</td>
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<tr>
<td>Pmpk/Plmax (%)</td>
<td>62 (sd 23.3)</td>
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<td>Authors</td>
<td>Measurements</td>
<td>Notes</td>
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<tr>
<td>A245</td>
<td>Collet et al 2007</td>
<td>IPM (cm H2O) 63 (sd 40.8)</td>
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<tr>
<td>A246</td>
<td>Chen et al 1989</td>
<td>Plm2 (cm H2O) 52.2 ± 16.8 Plm2/Plmax (%) 57.1 ±19.0</td>
<td>cohort Threshold loading B M</td>
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<tr>
<td>A247</td>
<td>Chen H-I et al 1985</td>
<td>Endurance time 11.2 ±0.8 min PTI 871 ±61 cm H2O min</td>
<td>Placebo controlled Threshold loading Sustained Inspiratory Pressure B+C1</td>
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<tr>
<td>A248</td>
<td>Chen et al 1989</td>
<td>IME (cm H2O.min) Midluteal (high progesterone) 815 ±43 Mid follicular (low progesterone) 649 ±62</td>
<td>Cohort Threshold loading C1 NK</td>
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<tr>
<td>A250</td>
<td>Newell et al 1989</td>
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<td>Unmatched healthy controls Max Static pressure C2</td>
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<tr>
<td>A261</td>
<td>McKeon et al 1986</td>
<td>After IMT all subjects able to tolerate smallest (2.5mm) aperture therefore ‘could be considered to have improved their IME’ cohort</td>
<td>Fixed orifice C1 LB</td>
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<tr>
<td>A262</td>
<td>Innes et al 1982</td>
<td>Rmax No data in results fig only</td>
<td>cohort Sustained pressure C1</td>
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<tr>
<td>A264</td>
<td>Ker et al 1996</td>
<td>Tlim sec 62.3 ±42</td>
<td>C1</td>
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**Ventilatory Muscle Endurance**

<table>
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<th>Ref</th>
<th>Authors</th>
<th>Measurements</th>
<th>Notes</th>
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<tr>
<td>A114</td>
<td>Nickerson et al 1982</td>
<td>SIP cm H2O 82 ±6</td>
<td>cohort Threshold loading C2 Nickerson &amp; Keens</td>
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<tr>
<td>A252</td>
<td>Levine et al 1992</td>
<td>MSVC L/min 25.0 ±3.6</td>
<td>cohort MSVC C2 LB</td>
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<tr>
<td>A254</td>
<td>Keenan et al 1995</td>
<td>Max Load (g) Mean (SD)</td>
<td>Matched Healthy Control Threshold loading B NK, M</td>
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Matched Healthy Control

Threshold loading B

NK, M
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<th>Condition</th>
<th>Control</th>
<th>Matched Controls</th>
<th>Notes</th>
<th>Sample Type</th>
<th>Raw Notes</th>
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<td>A255</td>
<td>Belman et al 1988</td>
<td>MSVC (L/min)</td>
<td>VMT</td>
<td>73.2 ±6.8</td>
<td>Control</td>
<td>63.9 ±5.4</td>
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<td>MSVC C2</td>
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<tr>
<td>A256</td>
<td>Martin et al 1982</td>
<td>MSVC L/min Arm</td>
<td>Leg</td>
<td>36 ±2</td>
<td>Control</td>
<td>63.9 ±5.4</td>
<td>Cohort</td>
<td>MSVC A</td>
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<tr>
<td>A257</td>
<td>Ries et al 1986</td>
<td>MSVC L/min Arm</td>
<td>46 ±5</td>
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<td>63.9 ±5.4</td>
<td>Cohort</td>
<td>MSVC A</td>
<td>LB</td>
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<tr>
<td>A258</td>
<td>Belman et al 1982</td>
<td>MSVC L/min Arm</td>
<td>Leg</td>
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<td>Cohort</td>
<td>MSVC A</td>
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<tr>
<td>A259</td>
<td>Silva et al 1998</td>
<td>70% MVV (L/min)</td>
<td>SCI</td>
<td>1.15</td>
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<td>14.60</td>
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<td>Bradley et al 1976</td>
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<td>Inselman et al 1993</td>
<td>MVV (L/min)</td>
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<td>A267</td>
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<td>Fixed resistance C2</td>
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<td>A268</td>
<td>Martin et al 1986</td>
<td>Pi time (sec)</td>
<td>11.9</td>
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<td>A270</td>
<td>Belman et al 1980</td>
<td>MSVC (L/min)</td>
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<td>A271</td>
<td>Keens et al 1977</td>
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<td>A272</td>
<td>Forte et al 1997</td>
<td>MSV (L/min)</td>
<td>141 ±7</td>
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### ‘Breathing Endurance’

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<th>A46</th>
<th>Peret et al 2000</th>
<th>1) Fig only no data in results</th>
<th>Unmatched healthy controls</th>
<th>Threshold loading</th>
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<td>Exp = 6.9 ±2.5</td>
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<td>Control = 6.2 ±2.2</td>
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<td>A59</td>
<td>Kohl et al 1997</td>
<td>70% MVV (min) 5.8 (SD 2.9)</td>
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<td>MVV A</td>
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<td>A26</td>
<td>Markov et al 1996</td>
<td>BE (sec) RMT 455 ±193 Control 293 ±143</td>
<td>RCT (training studies)</td>
<td>MVV A</td>
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<td>Boutellier et al 1992</td>
<td>Breathing Endurance (min) 6.1 (SD 1.8)</td>
<td>cohort</td>
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<td>LB</td>
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<td>A60</td>
<td>Boutellier et al 1992</td>
<td>BE (min) 4.2 (SD 1.9)</td>
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<td>A276</td>
<td>Martin et al 1982</td>
<td>MVV (l/min) Test 2(min) Athletes 172 ±11, Siblings 107 ±9</td>
<td>Sibling controlled</td>
<td>MVV A</td>
<td>LB</td>
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### Journal Search

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<tr>
<th>A278</th>
<th>Hill et al 2007</th>
<th>1) P'th.max (cmH20) IMT = 38.5 ±9.7 Sham = 40.5 ±18.3 2) Tlim Not stated fig only and percentage change after IMT</th>
<th>Double blind RCT (training study)</th>
<th>Threshold loading</th>
<th>NK, M</th>
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<tr>
<td>A279</td>
<td>Jardin et al 2007</td>
<td>RME (sec) Placebo 1205 ±957.2 Intervention 1161.2 ±1034.7 Significant increases in RME in both placebo and intervention.</td>
<td>cohort</td>
<td>Fixed Orifice C1</td>
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## Appendix 2.2

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<th>ID</th>
<th>Author</th>
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<th>Sample rate</th>
<th>Study Outcome</th>
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<tr>
<td>BFA 01</td>
<td>Lodrup - Carlsen (2000)</td>
<td>Review</td>
<td></td>
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<tr>
<td>BFA 02</td>
<td>Morris et al (2004)</td>
<td>Article</td>
<td>15 COPD</td>
<td>tPTEF/tE</td>
<td>Seated</td>
<td>100hz</td>
<td>Sig diff in tPTEF/tE between groups</td>
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<td></td>
<td></td>
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<td>16 Healthy</td>
<td>trsTidal</td>
<td>80seconds</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td>100hz</td>
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<td>BFA 03</td>
<td>Dotta et al (2007)</td>
<td>Article</td>
<td>Infants</td>
<td>tPTEF/tE</td>
<td>Spontaneous quite sleep without sedation</td>
<td>Not stated</td>
<td>Sig diff in tPTEF/tE between groups</td>
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<td></td>
<td></td>
<td></td>
<td>13 Congenital Diaphragmatic Hernia</td>
<td></td>
<td>60seconds</td>
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<td></td>
<td></td>
<td></td>
<td>28 healthy</td>
<td></td>
<td>Not stated</td>
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<td>BFA 04</td>
<td>Lum et al (2004)</td>
<td>Article</td>
<td>Infants</td>
<td>Behaviourally determined quite sleep after sedation</td>
<td>Not stated</td>
<td>n/a</td>
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<td></td>
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<td>29 healthy</td>
<td>Uses a restrictive ‘jacket’</td>
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<td>BFA 05</td>
<td>Lodrup - Carlsen et al (1997)</td>
<td>Article</td>
<td>Infants</td>
<td>tPTEF</td>
<td>Awake – semi-recumbent</td>
<td>250hz</td>
<td>Asthmatics had lower tPTEF than controls</td>
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<td></td>
<td></td>
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<td>24 healthy neonates</td>
<td></td>
<td>Time not given</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>26 asymptomatic children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 healthy controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BFA 06</td>
<td>Emralino et al (1997)</td>
<td>Article</td>
<td>Infants</td>
<td>79 healthy neonates</td>
<td>tPTEF</td>
<td>Sleeping non sedated</td>
<td>Recordings made until 4 repeatable TBFVL were gathered</td>
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<tr>
<td>BFA 07</td>
<td>Deerojanawong et al (2005)</td>
<td>Article</td>
<td>Infants</td>
<td>47 wheezing children</td>
<td>tPTEF/tE</td>
<td>Sleeping sedated</td>
<td>Four stable TBFV loops were selected</td>
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<tr>
<td>BFA 08</td>
<td>Devulapalli et al (2004)</td>
<td>Article</td>
<td>Young children</td>
<td>54 treated with inhaled steroids, 15 healthy controls</td>
<td>tPTEF/tE</td>
<td>Awake – quiet breathing</td>
<td>Four loops used- each loop chosen from 8 stored loops (max 32 breaths??)</td>
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<tr>
<td>BFA 09</td>
<td>Ranganathan et al (2003)</td>
<td>Article</td>
<td>Infants</td>
<td>47 Cystic Fibrosis, 95 Healthy controls</td>
<td>tPTEF/tE</td>
<td>Sleeping sedated – minimum 20 breaths during at least 2 periods of quite breathing</td>
<td>Not stated</td>
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<tr>
<td>BFA 10</td>
<td>Morris et al (1998)</td>
<td>Article</td>
<td>Adults</td>
<td>118 patients attending lung function lab with a diagnosis of airflow obstruction</td>
<td>Trs EV</td>
<td>Awake – ‘the first ten breaths’</td>
<td>80hz</td>
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<td>BFA 12</td>
<td>Bates et al (2000)</td>
<td>Review</td>
<td>Infants</td>
<td></td>
<td></td>
<td>The potential most troublesome aspect of tidal breathing from the computational point of view is the beginning and end of inspiration/expiration</td>
<td>50-100hz for timing and volume 200hz for tPTEF/tE</td>
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<tr>
<td>BFA 13</td>
<td>Williams et al (2000)</td>
<td>Article</td>
<td>64 children and young adults with CF</td>
<td>tPTEF/tE Trs S</td>
<td>Seated, 2 minutes</td>
<td>tPTEF/tE poor correlation with airflow obstruction</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>S = the slope of the whole post peak expiratory flow pattern)</td>
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<td></td>
<td>Totapally et al (2001)</td>
<td>Article</td>
<td>Twenty Infants &lt;1 year</td>
<td>tPTEF/tE TEF10 TEF25 TEF50</td>
<td>Sedated</td>
<td>Four loops used- each loop chosen from a minimum 16</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<td>No change in tPTEF/tE after bronchodilator, sig change in TEF10 and TEF25/PTEF</td>
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<td></td>
<td>Lodrup-Carlsen et al (1999)</td>
<td>Article</td>
<td>802 neonates 77 bronchiol obstruction 88 controls</td>
<td>tPTEF/tE</td>
<td>Awake</td>
<td>Four loops used- each loop chosen from 8 stored loops (max 32 breaths??)</td>
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<td></td>
<td>Not stated</td>
<td>No difference in tPTEF/tE</td>
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<td></td>
<td>Haland et al (2007)</td>
<td>Article</td>
<td>135 children at 2 years 90 studied</td>
<td>tPTEF/tE</td>
<td>Awake</td>
<td>Four loops used- each loop chosen from 8 stored loops With fR as low as possible</td>
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<td></td>
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<td>256hz</td>
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<td></td>
<td>Greengough et al (1998)</td>
<td>Article</td>
<td>85 infants 61 studied at =1 year 23/61 symptomatic wheezers</td>
<td>tPTEF/tE</td>
<td>Non sedated sleeping</td>
<td>First two consecutive periods of regular breathing each of at least 10 breaths</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>No difference in tPTEF/tE</td>
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</table>
| BFA 18 | Greengough et al (1998) | Article | 120 premature children assessed at mean 11 months | tPTEF/tE | Sedated  
Pneumotach  
First 10 regular breaths were used for analysis | - | Sig dif in tPTEF/tE who in neonatal period had not required mechanical ventilation, had not required increased inspired O2, and who were not symptomatic at follow-up. Suggest low tPTEF/tE independently associated with symptom status |
| BFA 19 | Hoo et al (1998) | Article | 108 preterm infants whose mothers had smoked in pregnancy | tPTEF/tE | Asleep  
60 consecutive regular breaths collected over 203 epochs | - | tPTEF/tE significantly lower in preterm infants exposed to tobacco inutero |
| BFA 20 | Stocks et al (1997) | Article | 56 preterm infants at discharge (mean 19 d)  
28 white/28 black | tPTEF/tE | Naturally asleep (no sedation)  
Inflatable jacket and Pneumotach | - | tPTEF/tE longer in black infants |
Respiratory Inductance Plethysmography | Not stated | Lower values of tPTEF/tE  
Associated with respiratory rate, age, maternal smoking during pregnancy, maternal hypertension during pregnancy and a family history of asthma |
| BFA 22 | Yuksel et al (1996) | Article | 60 term infants (mean 2 weeks) | tPTEF/tE | Non-sedated sleeping  
25 Flow loops from a pool of 60 | Not stated | 13 infants who became wheezy had a sig lower tPTEF/tE, however predictive value of tPTEF/tE is 41% limited use? |
| BFA 23 | Haland et al (2006) | Article | 616 children at birth and at 10 years of age | tPTEF/tE | Awake  
Four representative loops used | Not stated | Children whose tPTEF/tE at birth was at or below median were more likely at 10 year to have a history of |
<p>| XXXV | | | | | | | |
| BFA 24 | Habib et al (2003) | Article | 16 very low birth weight preterm infants (mean day 5) | Not clear awake/sleeping Pneumotach and chest wall sensor (+invasive balloon catheters) Collected in stretches 30-60sec | 100hz | tPTEF/tE higher than that reported in older infants. |
| BFA 25 | Dezateux et al (1994) | Article | 168 infants | tPTEF/tE Sedated sleep supine position Data collected in 30-60 sec epochs Data calculated from minimum of 20 breaths collected in 2 epochs | 100hz | In older infants (50 weeks) tPTEF/tE sig lower in those infants with lower respiratory illness with wheezing. Not seem in children at &lt;3months |
| BFA 26 | Ueda et al (1999) | Article | 64 healthy infants 19 had mothers who smoked during pregnancy | tPTEF/tE Sedated sleep 1x 20sec recording (approx 11 breaths) | Not stated | Dose response relationship between cigarettes smoked and lower tPTEF/tE |
| BFA 28 | Djupesland et al (1998) | Article | 17 healthy newborn | tPTEF/tE tPTEF Awake-pneumotachograph Four loops used- chosen from 8 stored loops | 256Hz | No difference between flow profiles from either right or left nostril |
| BFA 29 | Harrison et al (2009) | Article | 41 CF infants | tPTEF/tE sedated Pneumotachograph Time period not stated | Not stated | No correlation with tPTEF/tE and FEV |
| BFA 30 | Haland et al (2009) | Article | 607 birth cohort | tPTEF/tE Awake Pneumotachograph | 256Hz | Changes in tPTEF/tE from birth to 10years of age not sig. associated with lower respiratory tract |</p>
<table>
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<tr>
<th>BFA 31</th>
<th>Manczur et al 1999</th>
<th>Article</th>
<th>47 children 1 month-1 year</th>
<th>tPTEF/tE</th>
<th>Used Respiratory Inductance Plethysmography and pneumotachograph</th>
<th>Sampled first 10 ‘analysable’ breaths</th>
<th>Not stated</th>
<th>Both techniques can be used although result were significantly different. RIP is better tolerated</th>
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<tr>
<td>BFA 32</td>
<td>Black et al (2004)</td>
<td>Article</td>
<td>29 children 4-8 years with diagnosis of asthma.</td>
<td>tPTEF/tE</td>
<td>Used Respiratory Inductance Plethysmography</td>
<td>-</td>
<td>tPTEF/tE does not detect mild airway obstruction or response to bronchodilator provocation.</td>
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## Appendix 3.1

### Title of the invention:
Apparatus for determining respiratory muscle endurance of a person

### INT CL:
A61B 5/087 (2006.01)

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<th>0600295.4</th>
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<td>(22) Date of Filing:</td>
<td>12.07.2004</td>
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<td>(30) Priority Data:</td>
<td>(31) 0318349.0 (32) 11.07.2003 (33) GB</td>
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<td>(66) International Application Data</td>
<td>PCT/GB2004/003009 En 12.07.2004</td>
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<tr>
<td>(67) International Publication Data</td>
<td>WO2005/006800 En 27.01.2005</td>
</tr>
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<td>(43) Date of Publication:</td>
<td>17.05.2006</td>
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### UK CL (Edition X):
NOT CLASSIFIED

### Documents Cited:
- EP 1307994 A
- WO 1996/014115 A
- US 6015388 A
- US 3991304 A

### Field of Search:
As for published application 2420077 A viz:
- INT CL A61B
- Other
  updated as appropriate

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- Philip Jan Chowienczyk

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  LONDON, SE3 7LG, United Kingdom
Patient stops breathing

Energy = Power x Time

= Area under the curve

Endurance time

Time (minutes)

Power (Watts)
FIG 4

Patient stops breathing

Resistance (kPa/L/s)

Time (minutes)

Endurance time
APPARATUS FOR DETERMINING
RESPIRATORY MUSCLE ENDURANCE OF A PERSON

This invention relates to apparatus for determining respiratory muscle endurance of a person.

The respiratory muscle endurance of a person is important because it determines the person's susceptibility to developing serious breathing difficulties which may lead to respiratory failure and therefore death. The person's susceptibility to developing serious breathing difficulties is especially prevalent in persons with chronic lung disease, in whom impairment of respiratory muscle function often co-exists with disease of the person's lungs or airways.

There are known different types of apparatus for determining the respiratory muscle endurance of a person. These known types of apparatus comprise a mouthpiece through which the person inspires, and load-providing means for providing a pressure against which the person inspires. The endurance is measured as the duration for which respiration can be sustained by the person against the pressure. This pressure may be increased at set time intervals according to known and pre-defined protocols. The disadvantage of the known apparatus is that the work done against the pressure load, and hence the energy expended, depends upon the pattern of breathing of the person. This pattern of breathing tends to be unrepresentative of the person's usual pattern of breathing. This is because
the imposition of the fixed pressure load by the load-providing means is something that the person is not used to. For example, the person’s breathing pattern may vary if the load-producing means is a valve with an orifice which suddenly opens. Also for example, the person’s breathing pattern may depend upon whether the patient makes maximum or minimum effort on inspiration. Because the pattern of breathing is unrepresentative of the person’s usual pattern of breathing, interpretation of the results obtained by the known apparatus is difficult and may be inaccurate.

It is an aim of the present invention to reduce the above mentioned problem.

Accordingly, the present invention provides apparatus for determining respiratory muscle endurance of a person, which apparatus comprises a mouthpiece through which the person inspires, load-providing means for providing a pressure against which the person inspires, and pressure control means for controlling the pressure, the pressure control means being such that it controls the pressure in response to a breathing pattern of the person, and the apparatus being such that the load-providing means is a rotary valve having an orifice which is variable in size, and the pressure control means receives a first input in the form of air pressure from the patient’s mouth and a second input in the form of air flow from the patient’s mouth, characterized in that the apparatus then measures output energy from the patient’s mouth in the form of air pressure from the patient’s mouth x air flow from the patient’s mouth x time.
The apparatus of the present invention is able to be operated such that it is regulated according to the person's breathing pattern. This gives more accurate results in the determination of the respiratory muscle endurance of the person.

The rotary valve is preferably a servo-controlled cylindrical rotary valve.

The apparatus may be one in which the pressure control means comprises an electronic processor.

The processor may include a display screen. The processor may additionally or alternatively include a hard copy print-out means. Usually, the processor will be a micro-processor.

Preferably, the apparatus is one in which the measurements are obtainable as measurements at the mouthpiece. The measurements may be obtainable as measurements at positions other than the mouthpiece if desired.

Embodiments of the invention will now be described solely by way of example and with reference to the accompanying drawings in which:

Figure 1 shows apparatus for determining respiratory muscle endurance of a person;

Figure 2 shows in block diagram form the apparatus shown in Figure 1;

Figure 3 is a graph showing power plotted against time in order to give energy expended by a person; and

Figure 4 is a graph showing resistance plotted against time.
Referring to Figures 1 and 2, there is shown apparatus 2 for determining respiratory muscle endurance of a person. The apparatus 2 comprises a mouthpiece 4 through which the person inspires. The apparatus 2 also comprises load-providing means 6 for providing a pressure against which the person inspires. The apparatus further comprises pressure control means 8 for controlling the pressure. The pressure control means 8 is such that it controls the pressure in response to a breathing pattern of the person. This enables the breathing power in the form of pressure times flow to be controllable.

The pressure control means 8 comprises a valve 10 having an orifice which is variable in size. The valve 10 is a rotary valve which is servo-controlled by a motor 12. An electronic processor control circuit 14 controls operation of the motor 12. A pressure transducer 16 obtains pressure at the valve 10 and translates this pressure into electrical signals which are fed via a line 18 to the processor control circuit 14. In this way, the processor control circuit 14 is able to be fed with a first input in the form of the pressure at the valve 10.

A flow transducer senses the flow, and appropriate electrical signals are sent along line 22 as a second input for the processor control circuit 14.

As shown in Figure 2, the parts 10, 12, 14, 16, 18, 20, 22 form a controlled respiratory power transducer 24. The controlled respiratory power transducer 24 is connected to micro-processor control means 26 as shown.
The micro-processor control means 26 comprises a micro-processor circuit 28, display means 30 and a keypad 32. The micro-processor control circuit 28 is shown linked by line 34 to the processor control circuit 14. The processor control circuit 14 may be separate from or part of the micro-processor circuit 28.

Figure 1 shows the keypad 32. Figure 1 also shows the display means 30 in the form of a display screen 36 and a printer 38. The printer 38 gives a hard copy print out on paper 40.

Figure 3 shows power in watts plotted against time in minutes. Figure 3 also shows energy in the form of power times time which is equal to the area under the curve. Figure 3 also indicates endurance time and where a patient stops breathing. Figure 3 illustrates how, in one application, power is able to be progressively increased after a fixed interval of time according to a pre-defined protocol such that the total time taken for the test optimises the discriminatory function of the test for the condition of interest.

The apparatus 2 may alternatively be used to control resistance at a person’s mouth, this being in the form of pressure divided by flow. In this connection, Figure 4 shows resistance plotted against time.

It is to be appreciated that the embodiments of the invention described above with reference to the accompanying drawings have been given by way of example only and that modifications may be effected. Thus, for example, the shape of the mouthpiece 4 may be varied from that shown.
CLAIMS

1. Apparatus for determining respiratory muscle endurance of a person, which apparatus comprises a mouthpiece through which the person inspires, load-providing means for providing a pressure against which the person inspires, and pressure control means for controlling the pressure, the pressure control means being such that it controls the pressure in response to a breathing pattern of the person, and the apparatus being such that the load-providing means is a rotary valve having an orifice which is variable in size, and the pressure control means receives a first input in the form of air pressure from the patient's mouth and a second input in the form of air flow from the patient's mouth, characterized in that the apparatus then measures output energy from the patient's mouth in the form of air pressure from the patient's mouth x air flow from the patient's mouth x time.

2. Apparatus according to claim 1 in which the rotary valve is a servo-controlled cylindrical rotary valve.

3. Apparatus according to claim 1 or claim 2 in which the pressure control means comprises an electronic processor.

4. Apparatus according to claim 3 in which the electronic processor includes a display screen.
5. Apparatus according to claim 3 or claim 4 in which the electronic processor includes a hard copy print-out means.

6. Apparatus according to any one of claims 3 – 5 in which the electronic processor is a microprocessor.

7. Apparatus according to any one of the preceding claims in which the pressure and flow are obtainable as measurements at the mouthpiece.

8. Apparatus for determining respiratory muscle endurance of a person, substantially as herein described with reference to the accompanying drawings.
Apparatus for measuring the strength of a person's respiratory muscles

Apparatus (2) for measuring the strength of a person's respiratory muscles, which comprises a mouthpiece (4) for the person, a flow transducer (6), a pressure transducer (8), a variable orifice valve (10), a motor (12) for operating the variable orifice valve (10), and microprocessor control means (8), the microprocessor control means being such that it is able to control the motor (12) to cause the variable orifice valve (10) to vary its orifice size and thereby to maintain a constant predetermined pressure and enable the measurement of the flow rate generated by the person, or to maintain a constant predetermined flow rate and enable the measurement of the pressure generated by the person.
This invention relates to apparatus for measuring the strength of a person's respiratory muscles. The apparatus comprises a mouthpiece and a person is required to inhale against an obstruction in the apparatus in order to see what respiratory pressure the person can generate. This respiratory pressure is known as the maximum inspiratory pressure. The measurement of the maximum inspiratory pressure simply by inhaling against an obstruction does not give an in-depth understanding of the person's respiratory muscles. Such an in-depth understanding of the person's respiratory muscles would be advantageous in many situations. For example, with athletes, an in-depth understanding of the athlete's respiratory muscles could lead to a finding that the athlete's respiratory muscles were weak over a certain respiratory pressure range, and were strong over another respiratory pressure range. In this case, the athlete could then train his or her lungs especially over the weak respiratory pressure range, in order to strengthen the weak respiratory muscles. Also by way of example, it is mentioned that the majority of those people who die from major surgery actually die from respiratory failure. This is especially so if the major surgery is heart surgery. If an in-depth understanding of the person's respiratory muscles could be obtained before major surgery, then any weakness in the person's respiratory muscles could be identified. The person could then be given pre-operative exercises in order to strengthen their respiratory muscles over the weak respiratory pressure range or pressure ranges. This would then increase the person's chances of survival after major surgery because it would reduce the likelihood of that person dying from respiratory failure after the major surgery.

It is an aim of the present invention to provide apparatus which enables an in-depth understanding of a person's respiratory muscles to be obtained.

Accordingly, in one non-limiting embodiment of the present invention there is provided apparatus for measuring the strength of a person's respiratory muscles, which apparatus comprises a mouthpiece for the person, a flow transducer, a pressure transducer, a variable orifice valve, a motor for operating the variable orifice valve, and microprocessor control means, the microprocessor control means being such that it is able to control the motor to cause the variable orifice valve to vary its orifice size and thereby to maintain a constant predetermined pressure and enable the measurement of the flow rate generated by the person, or to maintain a constant predetermined flow rate and enable the measurement of the pressure generated by the person.

Usually, the flow rate or the pressure generated by the person will be generated by inhalation, but exhalation may be employed if desired.

Preferably, the apparatus of the invention will be used such that the microprocessor control means maintains different constant predetermined pressures, and measures the flow rate generated by the person at these constant predetermined pressures. If desired however, the apparatus of the present invention may be used such that the microprocessor control means maintains different predetermined flow rates and measures the pressure generated by the person. Either way, a maximum inspiratory pressure curve can be built up, and peaks of parts of the person's respiratory muscles can be seen from the curve. Corrective respiratory exercises can then be prescribed to strengthen any weak range or ranges of the respiratory muscles. For persons with weak respiratory muscles, the variable orifice will generally be large for the maximum inspired flow rate at a chosen pressure. Various exercises can be prescribed for persons with weak respiratory muscles over various ranges in order to improve the strength of the respiratory muscles over these ranges.

The apparatus may include a control circuit, the flow transducer being connected to the control circuit, the pressure transducer being connected to the variable orifice valve and to the control circuit, and the control circuit being connected to the microprocessor control means.

The microprocessor control means may comprise a microprocessor circuit, display means, and a keypad.

The display means may be a display screen and/or a hard copy print device.

Preferably, the mouthpiece has a flange at the end of the mouthpiece that goes into the person's mouth. The flange helps the person's mouth to seal around the mouthpiece during the inhalation.

Preferably, the variable orifice valve is a rotary variable orifice valve. With such a rotary variable orifice valve, friction may be independent of applied pressure. The relationship between the resistance to flow and rotation of the valve is able easily to be adjusted by the shape of the orifice.

The rotary variable orifice valve may have an orifice which is of a shape that causes the resistance to flow of the rotary variable orifice valve to increase with rotation. Preferably, the orifice in the rotary variable orifice valve is of a triangular shape. Other shapes may be employed if desired.

The rotary variable orifice valve may comprise a cylindrical member and a sleeve which is a rotational fit with respect to the cylindrical member. The sleeve will normally be a rotational fit over the cylindrical member.

The rotary variable orifice valve may be one in which the cylindrical member has an aperture, the sleeve has the orifice, and the aperture and the orifice are positioned such that they overlap as the sleeve rotates. Alternatively, the rotary variable orifice valve may
be one in which the cylindrical member has the orifice, the sleeve has an aperture, and the aperture and the orifice are positioned such that they overlap as the sleeve rotates. Alternatively, the rotary variable orifice valve may be one in which the orifice is positioned partly in the cylindrical member and partly in the sleeve.

[0016] Other types of rotary variable orifice valve may be employed so that, for example, the rotary variable orifice valve may be one in which the cylindrical member rotates and the sleeve remains stationary.

[0017] The variable orifice valve may be other than a rotary variable orifice valve. Thus, for example, the variable orifice valve may be a flat plate variable orifice valve. The flat plate variable orifice valve may cause friction which is dependent upon the amount of pressure being placed upon the plate. This friction may need to be overcome by the use of a motor which is larger than the motor required for a rotary variable orifice valve which does not suffer from generated friction. The use of a smaller motor may in turn enable the apparatus of the present invention to be produced in a smaller size. Alternatively or in addition, any battery power employed to drive the motor may be less for a rotary variable orifice valve than for a flat plate orifice valve.

[0018] Embodiments of the invention will now be described solely by way of example and with reference to the accompanying drawings in which:

Figure 1 shows first apparatus of the present invention;

Figure 2 is a block circuit diagram of the apparatus shown in Figure 1;

Figure 3 shows a curve obtained by measuring pressure against flow and obtaining maximum inspired flow rates for different pressures; and

Figure 4 is a perspective view of a rotary variable orifice valve which is able to be used in the apparatus shown in Figure 1.

[0019] Referring to Figures 1 and 2, there is shown apparatus 2 for measuring the strength of a person's respiratory muscles. The apparatus 2 comprises a mouthpiece 4 for being inhaled through by the person, a variable orifice valve arrangement 6, and microprocessor control means 8. The variable orifice valve arrangement 6 comprises a variable orifice valve 10 and a motor 12 for operating the variable orifice valve 10. The microprocessor control means 8 is such that it is able to control the motor 12 to cause the variable orifice valve 10 to vary its orifice size and thereby to maintain a constant predetermined pressure and enable the measurement of the flow rate generated by the person, or to maintain a constant predetermined flow rate and enable the measurement of the pressure generated by the person.

[0020] The variable orifice valve arrangement 6 also comprises a control circuit 20 and a pressure transducer 22. A flow transducer 18 is positioned between the mouthpiece 4 and the variable orifice valve arrangement 6.

[0021] The constant respiratory pressure transducer 6 is connected to the microprocessor control means 8 by a lead 14 as shown in Figure 1.

[0022] During use of the apparatus 2, for a person with weak lungs, the orifice in the variable orifice valve 10 will usually be relatively small for the maximum inspired flow rate. For a person with strong lungs, the orifice in the variable orifice valve 10 will usually be relatively large for the maximum inspired flow rate. Measurements can be taken of pressure against flow in order to build up a maximum inspiratory pressure curve 16 as shown in Figure 3. If the measurements being taken fluctuate due to uneven inhalation by the person, then a suitable algorithm may be employed to provide an average for each measurement. The curve 16 is then useful for identifying areas of weakness in the person's respiratory muscles. The person, for example a patient shortly to undergo major heart surgery, or an athlete, can then be given remedial exercises to strengthen their respiratory muscles over the weak range or ranges. In the case of persons about to undergo major surgery, the improved respiratory muscles will increase their chances of survival. In the case of athletes, improved respiratory muscles may result in improved performances.

[0023] As shown in Figure 2, the flow transducer 18 is connected to the control circuit 20. The pressure transducer 22 is connected to the variable orifice valve 10 and to the control circuit 20. The control circuit 20 is connected to a microprocessor circuit 24 of the microprocessor control means 8. The microprocessor circuit 24 is also connected to display means 26 and a keypad 28.

[0024] As shown in Figure 1, the display means 26 comprises a display screen 30 and a hard copy print device 32. The display screen 30 is shown displaying a maximum inspiratory pressure curve 16. The print device 32 is shown having provided a hard copy print 34.

[0025] The mouthpiece 4 has a flange 36 at the end of the mouthpiece that goes into the person's mouth. The flange 36 helps the person's mouth to seal around the mouthpiece 4 during inhalation. The other end 38 of the mouthpiece 4 is cylindrical for being a push fit over a cylindrical part of the constant respiratory pressure transducer 6.

[0026] Figure 4 shows a rotary variable orifice valve 42 which is a preferred form of the variable orifice valve 10 shown in Figure 1. The rotary variable orifice valve 42 does not generate friction so that friction is independent of applied pressure. The relationship between resistance to flow and rotation of the valve is easily adjusted by adjusting the shape of an orifice 44. The orifice 44 is of a shape that causes the resistance to flow of the rotary variable orifice valve 42 to increase with rotation. More specifically, the orifice 44 is of a triangular shape as shown.

[0027] The rotary variable orifice valve 42 comprises
a cylindrical member 46 having a bore 48 and a rectangular aperture 50. The orifice 44 is in a sleeve 52 which is a rotational fit over the cylindrical member 46. As shown in Figure 4, the cylindrical member 46 is in the form of a short tube. During use of the rotary variable orifice valve 42, the sleeve 52 rotates over the cylindrical member 46, and the orifice 44 overlaps by varying amounts the rectangular aperture 50. In this way, the effective size of the orifice 44 is varied. Air flow along the bore 48 and through the orifice 44 is shown by arrows.

[0027] The rotation of the sleeve 52 is controlled by the motor 12. The motor 12 is mounted on one side of the sleeve 52. The motor 12 has a pulley 54 which drives an endless drive belt 56. The drive belt 56 is in frictional engagement with the outside of the sleeve 52 as shown. Thus rotation of the pulley 54 clockwise or anti-clockwise, causes a corresponding rotation of the sleeve 52 via the drive belt 56. The motor 12 is mounted on a motor mounting plate 58.

[0028] It is to be appreciated that the embodiments of the invention described above with reference to the accompanying drawings have been given by way of example only and that modifications may be effected. For example, with reference to Figure 4, the motor 12 may be arranged to drive the sleeve 56 by means other than the drive belt 56. Thus, for example, the drive could be via toothed wheels. Also, if desired, the motor 12 could be mounted in line with the cylindrical member 46 and then connected to the sleeve 52 by an appropriate drive arrangement. Instead of using the rotary variable orifice valve 42, the variable orifice valve 10 may be a flat plate variable orifice valve. Such a flat plate variable orifice valve 10 will generate a certain amount of friction during the measurement of the maximum inspiratory pressure, and this friction may need to be overcome, for example with a larger motor 20, or stronger batteries for driving the motor used in the apparatus of the invention. Alternatively, or in addition, the motor may be mains operated. In Figure 3, the curve 16 has been obtained by causing the microprocessor control means 8 to control the motor 12 to cause the variable orifice valve 10 to vary its orifice size and thereby to maintain constant predetermined pressures, so that the flow rate generated by the person can be measured. If desired however, the curve 16 may be obtained by causing the microprocessor control means 18 to control the motor 12 to cause the variable orifice valve 10 to vary its orifice size and thereby to maintain constant predetermined flow rates, so that the pressure generated by the person can be measured.

Claims

1. Apparatus for measuring the strength of a person’s respiratory muscles, which apparatus comprises a mouthpiece for the person, a flow transducer, a pressure transducer, a variable orifice valve, a motor for operating the variable orifice valve, and microprocessor control means, the microprocessor control means being such that it is able to control the motor to cause the variable orifice valve to vary its orifice size and thereby to maintain a constant predetermined pressure and enable measurement of the flow rate generated by the person, or to maintain a constant predetermined flow rate and enable the measurement of the pressure generated by the person.

2. Apparatus according to claim 1 and including a flow transducer, the flow transducer being connected to the control circuit, the pressure transducer being connected to the variable orifice valve and to the control circuit, and the control circuit being connected to the microprocessor control means.

3. Apparatus according to claim 1 or claim 2 in which the microprocessor control means comprises a microprocessor circuit, display means, and a keypad.

4. Apparatus according to claim 3 in which the display means is a display screen and/or a hard copy print device.

5. Apparatus according to any one of the preceding claims in which the mouthpiece has a flange at the end of the mouthpiece that goes into the person’s mouth.

6. Apparatus according to any one of the preceding claims in which the variable orifice valve is a rotary variable orifice valve.

7. Apparatus according to claim 6 in which the rotary variable orifice valve has an orifice which is of a shape that causes the resistance to flow of the rotary variable orifice valve to increase with rotation.

8. Apparatus according to claim 6 or claim 7 in which the orifice in the rotary variable orifice valve is of a triangular shape.

9. Apparatus according to any one of claim 6 - 8 in which the rotary variable orifice valve comprises a cylindrical member and a sleeve which is a rotational fit over the cylindrical member.

10. Apparatus according to claim 9 in which the cylindrical member has an aperture, the sleeve has the orifice, and the aperture and the orifice are positioned such that they overlap as the sleeve rotates.

11. Apparatus according to claim 9 in which the cylindrical member has the orifice, the sleeve has an aperture, and the aperture and the orifice are posi-
tioned such that they overlap as the sleeve rotates.

12. Apparatus according to claim 9 in which the orifice is positioned partly in the cylindrical member and partly in the sleeve.

13. Apparatus according to any one of claims 1 - 5 in which the variable orifice valve is a flat plate variable orifice valve.
## DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
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The present search report has been drawn up for all claims.

**THE HAGUE**

15 October 2003

Visser, R
### ANNEX TO THE EUROPEAN SEARCH REPORT

**EP 1 397 994 A1**

**ON EUROPEAN PATENT APPLICATION NO.**

EP 03 25 5560

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. All the members are as contained in the European Patent Office ESP 1 file. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-10-2003

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For more details about this annex, see Official Journal of the European Patent Office, No. 12/92

11
Appendix 7.1

Respiratory Research – Feedback Form

Please circle 1 answer per question

Regards current studies into respiratory diseases:

1. It is important for me to know what research is being carried out.
   Agree 1 2 3 4 5 6 7 Disagree

2. I would like to be consulted on what research should be undertaken
   Agree 1 2 3 4 5 6 7 Disagree

3. It is important for the research to take place
   Agree 1 2 3 4 5 6 7 Disagree

4. I would be happy to be asked to consider taking part in a research study
   Agree 1 2 3 4 5 6 7 Disagree

Measurement of respiratory function

5. I have undertaken tests that measure how my lungs work Yes No

6. I found these:
   Easy 1 2 3 4 5 6 7 Hard

7. If you have any other comments please make below:
Appendix 7.2

Breathing Energy Expenditure in Chest Disease Patients

A collaboration between the Department of Respiratory Medicine

Cwm Taf NHS trust and the Glamorgan Clinical Physiology Unit at the
University of Glamorgan
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1.0 Research Team

Principal Investigator: Dr Paul Neill
Investigators: Dr Mark Williams, Mr Tom Powell

Royal Glamorgan Hospital
University of Glamorgan

2.0 Rationale for proposed study

A variety of ways have been developed to quantify endurance properties of respiratory muscles. These generally involve asking individuals to breathe maximally or progressively against a load until the point of fatigue, with this point depending heavily on subject motivation and compliance. It has long been recognised that there is a need for better techniques for evaluating respiratory muscle endurance and work capacity in patients with obstructive chest disease (Clanton, 1995).

We propose a new 6-minute non-volitional test, during which study participants will breath against a constant resistive load. We utilise a device that can apply a resistive load throughout tidal breathing, both on inspiration and expiration. By incorporating a flow measurement head and differential pressure sensor, the device samples pressure and flow at 100Hz and uses this to continually adjust its internal diameter to ensure that irrespective of flow generated, the applied resistance remains constant. Sampling pressure and flow allows us to calculate energy needed to move the volume of air whilst breathing through this device.

We define this outcome as breathing energy expenditure (BEE) and express it in terms of joules of energy per litre of inspired air (J.L⁻¹). Put simply, it is the amount of work performed by the respiratory system and we believe it can provide a measure of functional respiratory endurance in a non-volitional way.

This seated 6-minute test offers an improvement on existing techniques as it is non-invasive, non-volitional and does not require maximal effort on behalf of the subjects and is of a shorter duration than most maximal tests of respiratory endurance function. In mild to severe COPD, resting lung function is often compromised and patients alter their breathing pattern to minimise their work of breathing. This new approach could therefore be of particular benefit in patients with respiratory diseases such as COPD. We plan to control the pattern of breathing of study subjects using a bespoke metronome that allows the ratio of inspiratory and expiratory time to be set independently of the breath per minute rate.

We have already performed this test in healthy control subjects, completing over 200 separate trials, during which no adverse events or other difficulties were reported. In addition our research team has recently received approval to use this technique to measure BEE as part of a wider ranging study with COPD patients.

This study will allow us to gain a better insight into the mechanics of endurance breathing in patients with chest disease, possibly leading to a non-volitional, effort independent test of functional respiratory status. This may ultimately lead to a better understanding of functional respiratory status, and inform clinical treatment and management of the patient with respiratory disease.

3.0 Objectives and Aims

The primary aim of this study is to investigate whether responses to constant loaded breathing in patients with chest disease are similar to that in healthy subjects already studied. The study will test the hypothesis that patients with chest disease will have a greater BEE than healthy subjects at rest, and that BEE assessment with this technique may provide a useful tool in assessing patients with
chest disease. The secondary aim of this study will be to assess the utility of a new method to control the pattern of breathing in patients with chest disease.

4.0 Participants

Prospective participants will be patients attending out-patients clinics for assessment of their pulmonary lung function within the Department of Respiratory Medicine at the Royal Glamorgan Hospital. All these patients, who will be under the care of Dr Paul Neill and colleagues will, after informed consent has been obtained (Section 4.2), be assessed and screened using study inclusion and exclusion criteria (Section 4.3 & 4.4) that will be recorded using the study screening form (Appendix I).

4.1 Recruitment of Participants

Prospective participants will be as normal, contacted by letter prior to their appointment at the pulmonary lung function clinic. This letter will also contain a copy of the study information sheet for their attention that will outline the study (appendix II). On arrival prospective participants will be asked whether they would be interested in taking part. Patients who express an interest in the proposed study will have it explained to them in detail during which they will have the opportunity to ask questions, what they can expect and what is expected of them. If they are happy to take part informed consent will be taken.

4.2 Informed Consent

Informed Consent will be secured from all participants before any study investigations take place. If they are happy to take part participants will be asked to sign a Study Informed Consent Form (appendix III) a copy will be given to the participant, one to be kept with the clinical record form and the original being retained in the patients Medical Notes. As a matter of course every patients GP will be informed by letter of their participation (appendix IV). Once informed consent is given participants will be screened using study inclusion and exclusion criteria (4.3 & 4.4).

4.3 Inclusion Criteria

Clinically defined obstructive or restrictive respiratory disease

Clinically stable — not currently receiving prescribed medication for an exacerbation of their disease symptoms

- free from exacerbation of their respiratory disease for a period of at least 2 weeks

No significant unstable disease co-morbidity’s

Capable of providing informed consent.

Willing for GP to be informed of participation in study

Willing to take part in all study measurements.

4.4 Exclusion Criteria

Any history of severe unstable disease co-morbidity’s.

Any other serious medical condition

Any prescribed medical condition (unless associated with respiratory disease status)

Pregnancy
Inability to complete study measurements
Significant visual or audiological impairment

5.0 Study Parameters to be Assessed

1. Breathing Profile (Colasanti et al. 2004)
   - Total breath duration - seconds
   - Duration of inspiration and expiration - seconds
   - Peak inspiratory and expiratory flow - litres per second
   - Timing of peak inspiratory and expiratory flow - seconds
   - Expiratory flow profile - angle
   - Tidal volume - litres
   - Resting Respiratory Breathing Rate - respirations per minute

2. Questionnaires of Dyspnoea Measurement (Appendix V)
   - Medical Research Council Breathlessness Score (Bestall et al. 1999)
   - St Georges Respiratory Questionnaire

3. Specific Respiratory Muscle Function (Powell et al. 2007)
   - Respiratory Muscle Endurance - BEE (Joules/Litre)

5.1 Clinical History
In addition to study measurements after the screening, informed consent and study measurement processes but whilst still in possession of a participants medical notes, the following information will be recorded.

- Height - metres
- Weight - kilograms

- Forced Expiratory Volume in 1 second (FEV₁) - litres sec⁻¹
- Forced Vital Capacity (FVC) - litres
- Maximal Inspiratory Mouth Pressure (MIP) - centimetres of water (cmH₂O)
- Medication History
  - current medications
  - number of IV/oral antibiotic courses in the previous year
- Clinical Visit history
  - number of out-patient attendances in previous year
- number of in-patient attendances in previous year
- Pulmonary Function Test history
  - best lung function in previous year (if undertaken)
  - result of previous six minute walk test (if undertaken)
- Blood Gas History
- haemoglobin concentrations

5.2 Calibration and Hygiene

All equipment used in study measurements will be calibrated and maintained to ensure accuracy of results. All protocols to ensure hygiene of equipment will be strictly adhered to, for example single use mouth pieces and filters for spirometry.

6.0 Location of Study Investigations

It is intended that all study investigations will be undertaken within the Department of Respiratory Medicine at the Royal Glamorgan Hospital.
7.0 Flow chart of patient participation

Study Information sheet included with Lung Function clinic letter

Willing to take part?

Yes

Informed Consent Taken

5-10 min

No

No further action

Screening of Patient

Fulfil Inclusion Criteria?

Yes

1. Breathing patterns

1-2 min

2. Dyspnoea questionnaires

2 - 4 min

3. Functional Respiratory Endurance Measurements

24 min

4. End of Session

Total Time 40 min
8.0 Primary Outcomes

The primary outcome of this study will be the level of BEE at constant applied resistances to breathing, and any relationship to existing methods of pulmonary function assessment. Secondary outcomes will be utility of a bespoke metronome to control breathing pattern.

9.0 Number of Participants and Power Calculations

This study will be used to help provide a better estimate of the number of participants needed to gain statistical accuracy for possible future studies. Typically other recent studies in this area have used study samples of 20 – 50 patients (Cardoso et al. 2007; Su et al. 2007; Rosa et al. 2006), often based around pulmonary rehabilitation programmes, retrospective studies normally have much larger sample sizes [n >100]. As such we plan to recruit only a limited number of subjects (minimum of 30) and use the results to inform further study.

10.0 Statistical Analyses

Simple descriptive statistics will be used to describe the participant population. Using computer statistical software package (SigmaStat V3), parametric statistical testing will be used to assess for statistical differences. Regression analysis will be used to define trends and correlation within the data.

11.0 Anonymisation and Data Management

All participants will be anonymised and assigned a study number that will be used to identify them in all forms of data storage. Tom Powell and/or Dr Paul Neill will be responsible for allocating each successfully screened participant a study number. This will be used to identify the participant and associated data at all times. Dr Neill will securely hold the master list of patient names and corresponding numbers in a locked filing cabinet in his office at the Department of Respiratory Medicine.

Data analysis will be conducted at the University of Glamorgan, by members of the study team. All collected data will be kept securely stored both in paper form and electronically on password protected computers. A hard copy of all data will also be securely kept in case of electronic de-integrity in locked filing cabinets. Only members of the research team (Section 1.0) will have password access to study computers and all paper copies will be kept in filing cabinets in locked offices to which only members of the study team will have access.

12.0 Ethical Considerations

All participants will have their breathing profile patterns and functional respiratory endurance measured. These are simple, non-invasive tests that have already been ethically approved and undertaken in healthy individuals and in patients with COPD. There have been no reported adverse events as a result of undertaking these tests and we believe them to be safe to be used in the proposed study population.

Any participation in research requires those taking part to deviate from their normal routine and that doing so will cause them to experience some inconvenience and this study is no different. Participants will already be undertaking spirometry as part of routine clinical treatment. Pulmonary function tests require maximum effort and co-operation during repeated attempts over a period of time. Such a high degree of effort in a relatively short period of time can result in short term fatigue, coughing, breathlessness and short duration discomfort, all of which become more pronounced in chest disease patients.
The 6-minute test we propose is of a sub-maximal, non-volitional nature, in effect the pulmonary tests the participants will be undertaking will be a significantly more intense experience than the proposed study tests that we liken to breathing at rest. Participants will have the option to halt study tests at any point for any reason, however the level of applied resistive load will be such that in our experience it would be extremely unlikely for this to occur.

There are no obvious risks that will result from participation in this study, and we feel that screening measures put in place will further reduce any possible causes of harm. No long term side-effects due to participation are envisaged or anticipated.

13.0 Time-scale

It is expected that from recruitment of the first participant to completion of testing of the last participant will be a period of no longer than 12 months.

14.0 Dissemination of Results

Findings of this study will be disseminated verbally at national and international scientific meetings and in print in scientific peer-reviewed journals.

15.0 References


Cardoso, F. Tufanin, AT. Colucci, M. Nascimento, O & Jardim, JR. Replacement of the 6-minute walk test with maximal oxygen consumption in the BODE index applied to patients with Chronic Obstructive Disease (COPD). 2007. Chest [May 15th].


Powell, T & Williams, EM. Is paced breathing important when applying a constant resistance test? Thorax. 2007: A95-P86.


**Appendix I – Study Screening Form**

Breathing Energy Expenditure in Chest Disease Patients

**Study Screening Form**

1. **Inclusion Criteria**

   FEV1 _______ pFEV1 _______
   FVC _______ pFVC _______
   FEV1/FVC ______%  
   GOLD Status

   Current Medication
   •
   •
   •

   Date of last COPD exacerbation _______ (more than 12 months? Yes / No)

   Capable of Providing informed Consent Yes / No

   Able to attend study investigation sessions Yes / No

   Willing for GP to be informed of participation in study Yes / No

   Willing to take part in all study measurements Yes / No

2. **Exclusion criteria**

   Any history of severe disease co-morbidity? Yes / No

   Any other serious medical condition? Yes / No

   Any prescribed medication? (unless associated with COPD disease status) Yes / No

   Pregnancy? Yes / No / NA

   Unable to complete 6MWD ? Yes / No

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1 November 2007

7)
Appendix II – Study Information Sheet

Department of Respiratory Medicine
Cwm Taf NHS Trust

University of Glamorgan
Faculty of Health, Sport and Science

Dr Paul Neill
Tel: 01443 443 443 ext.3544
E-mail: Paul.Neill@pr-tr.wales.nhs.uk

Tom Powell
Tel: 01443 483084
E-mail: tpowell@glam.ac.uk

Breathing Energy Expenditure in Chest Disease Patients

Study Information Sheet — Part 1

You are being invited to take place in a research study, before you decide to participate, it is important for you to read the following information, to understand why the research is being undertaken and what is involved. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

What is the purpose of this study

There are many different tests that measure how your lungs work, many of these require a lot of effort and can leave you feeling breathless. We are interested in developing a new technique that assesses the endurance capacity of your lungs and how much energy it takes, whilst you are breathing in a more relaxed manner.

Why have I been asked to participate?

You have been asked to participate as you have been referred to the lung function clinic at the Royal Glamorgan Hospital. We will be asking approximate 30 other people like yourself to take part as well. We think you will be able to complete all the study assessments.

Do I have to take part?

No, taking part is voluntary. It is up to you to decide whether or not to take part. If you do decide to take part we will ask you to sign a consent form and give you a copy of this information sheet and the consent form to keep.

What will happen to me if I take part?

During your visit to the Department of Respiratory Medicine at the Royal Glamorgan hospital for assessment of your lung function you will be asked if you want to take part in the study. We will answer any questions you may have about the study. There will only be 1 session as part of this study that should take approximately 30-40 minutes to complete.

What will I have to do if I take part?

If you agree to enter the study you will undertake some breathing tests whilst sitting down. These tests are simple to complete and we think you will be able to complete them.
What are the possible disadvantages and risks of taking part?
During the breathing tests you may become breathless, however this should not last long and will soon pass. The breathing tests will be similar to those which you will be doing as part of your visit to the lung function clinic.

What are the possible benefits of taking part?
There are no direct benefits to you from taking part. We hope that study findings will help increase our understanding of chest disease and may help in the development of future treatments and care.

What if there is a problem?
Any complaint about the way in which you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2 of the information sheet.

Will my taking part in this study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in part 2 of this information sheet.

Part 2
What will happen if I don't want to carry on with the study?
If you decide to take part you are still free to withdraw at any time. If you decide not to take part you do not have to give a reason, nobody will be upset and the standard of care you receive will not be affected.

What if there is a problem?
If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed by someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Will my taking part in this study be kept confidential?
Yes. You will be anonymised and assigned a study number which will mean you can’t be identified in the study results. Additionally if you consent to take part in the research your medical records may be inspected by members of the study research team. Your name will not be disclosed outside the hospital although, with your permission, your GP will be informed you will be taking part.
What will happen to the results at the end of the research study?
The results of the study will be presented to local, national and international medical meetings. The results will also be reported in a medical journal, you will not be identified in any of these reports.

Who is organizing and funding this research?
This study is being led by Dr Paul Neill and sponsored by the Cwm Taf NHS trust. We will not receive any payments or funding for including you in this study.

Who has reviewed the study?
This study has been looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favorable opinion by the South East Wales Research Ethics Committee. It has also been reviewed by the University of Glamorgan and Cwm Taf NHS Trust.

Where can I get independent advice about taking part in research?
INVOLVE is a national advisory group funded by the Department of Health which aims to promote and support active public involvement in NHS, public health and social care research. INVOLVE was established to promote public involvement in research in order to improve the way research is prioritized and commissioned undertaken communicated and used. You can contact INVOLVE by: Tel: 02380 651 088, e-mail: admin@invo.org.uk, Post: Involve, Wessex House Eastleigh, Hampshire, S050 9FD.

Who do I contact now?
You will be contacted by a study investigator on arrival at the Lung Function clinic at the Royal Glamorgan Hospital, who will ask if you wish to take part. Remember you do not have to take part and may withdraw at any time. If you would like to contact a member of the research team to ask any questions regarding the study you can contact Dr Paul Neill (Tel 01443 443 443 ex 3544).

Thank you for taking the time to read the information sheet
Appendix III - STUDY CONSENT FORM

Department of Respiratory Medicine
Cwm Taf NHS Trust

University of Glamorgan
Faculty of Health, Sport and Science

Dr Paul Neill
Tel: 01443 444 443 ext. 3544
E-mail: Paul.Neill@pr-tr.wales.nhs.uk

Tom Powell
Tel: 01443 483084
E-mail: tpowell@glam.ac.uk

STUDY CONSENT FORM

Centre Number:
Study Number:
Patient Identification Number for this trial:


Please initial box

1. I confirm that I have read and understand the information sheet dated May 2008 for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical or legal rights being affected.

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities of from the NHS trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

4. I agree to my GP being informed of my participation in the above study.

5. I agree to take part in the above study.

Name of Participant _______________ Date ___/____/____ Signature _______________

Name of Researcher _______________ Date ___/____/____ Signature _______________

1 copy to CRF, 1 copy to be given to participant, 1 copy to patients GP, Original to patients notes

V3.2 May 2008

LXXVI
Dear Dr

Re:

Address:

Your patient is taking part in a pilot study to investigate breathing energy expenditure in chest disease patients using a new method of generating constant resistive breathing loads.

If you have any questions please do not hesitate to contact Dr Paul Neill at the Department of Respiratory Medicine tel: 01443 443 443 ext 3544.

Many thanks

Yours sincerely

Dr Paul Neill

Tom Powell
Appendix V Study Questionnaires

MRC DYSPNOEA SCALE

Subject ID _____ Date ___/___/____

1, “I only get breathless with strenuous exercise”

2, “I get short of breath when hurrying on the level or up a slight hill”

3, “I walk slower than people of the same age on the level because of Breathlessness or have to stop for breath when walking at my own pace on the level”

4, “I stop for breath after walking 100 yards or after a few minutes on the level”

5, “I am too breathless to leave the house”

MRC dyspnea score V1 November 2007 TP
ST. GEORGE’S RESPIRATORY QUESTIONNAIRE

Study Number:

Date:

Symptom Score:

Activities Score:

Impact Score:

Total Score:

V2 May 2008
Part 1

These are questions about how much chest trouble you have had over the last month of the year.

Please mark the appropriate box by filling in the box with a thick pencil line.

<table>
<thead>
<tr>
<th>Question</th>
<th>Most days a week</th>
<th>Several days a week</th>
<th>A few days a month</th>
<th>Only with chest infections</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Over the last month, I have coughed:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Over the last month, I have brought up phlegm (sputum):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Over the last month, I have had shortness of breath:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Over the last month, I have had attacks of wheezing:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. During the last year, how many severe or very unpleasant attacks of chest trouble have you had:</td>
<td>More than 3 attacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 attacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 attacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 attack</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>no attacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. How long did the worst attack of chest trouble last: (go to question 7 if you had no severe attacks)</td>
<td>A week or more</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 or more days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 or 2 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less than a day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Over the last year, in an average week, how many good days (with little chest trouble) have you had:</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 or 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 or 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>nearly every day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>every day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. If you have a wheeze, is it worse in the morning:</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Version 2 May 2008
PART 2

Please mark the appropriate box by filling in the box with a thick pencil line

How would you describe your chest condition:
the most important problem I have……………………………….  
causes me quite a lot of problems……………………………….  
causes me a few problems………………………………………..  
causes no problems……………………………………………..  

If you ever had paid employment, please mark one of these:
my chest trouble made me stop work…………………………..  
my chest trouble interferes with my work or made me change my work……  
My chest trouble does not affect my work……………………  

SECTION 2
Questions about what activities usually make you feel breathless. Please mark each question TRUE (T) or FALSE (F) as applies to you these days:
sitting or lying still……………………………………………  T  F  
getting washed or dressed………………………………………  T  F  
walking around the home………………………………………..  T  F  
walking outside on the level…………………………………….  T  F  
walking up a flight of stairs……………………………………….  T  F  
walking up hills………………………………………………….  T  F  
playing sports or games………………………………………..  T  F  

SECTION 3
Some more questions about your cough and breathlessness. Please mark each questions TRUE (T) or FALSE (F) as applies to you these days:
my cough hurts………………………………………………….  T  F  
my cough makes me tired…………………………………………  T  F  
I am breathless when I talk……………………………………….  T  F  
I am breathless when I bend over………………………………  T  F  
my cough or breathing disturbs my sleep………………………..  T  F  
I get exhausted easily…………………………………………..  T  F  

Version 2 May 2008
SECTION 4
Questions about other effects that your chest trouble may have on you. Please mark each question TRUE (T) or FALSE (F) as applies to you these days:

my coughing or breathing is embarrassing in public

my chest trouble is a nuisance to my family, friends or neighbours

I get afraid or panic when I cannot get my breath

I feel that I am not in control of my chest problems

I do not expect my chest to get any better

I have become frail or an invalid because of my chest

exercise is not safe for me

everything seems too much of an effort

SECTION 5
Questions about your medication. If you are receiving no medication go straight to Section 6.

my medication does not help me very much

I get embarrassed using my medication in public

I have unpleasant side effects from my medication

my medication interferes with my life a lot

SECTION 6
These are questions about how your activities might be affected by your breathing. Please mark each question TRUE (T) or FALSE (F) which you think applies to you because of your breathing.

I take a long time to get washed or dressed

I cannot take bath or shower, or I take a long time

I walk slower than other people, or I stop for rests

jobs such as housework take a long time, or I have to stop for rests

if I walk up one flight of stairs, I have to go slowly or stop

if I hurry or walk fast, I have to stop or slow down

my breathing makes it difficult to do such as walk up hills, carrying things up stairs, light gardening such as seeding, dance, play bowls or play golf
SECTION 6 (cont.)
my breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim………….

T F

my breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports…………………………………………………..

T F

SECTION 7
We would like to know how your chest usually affects your daily life. Please mark each question TRUE (T) or FALSE (F) which you think applies to you because of your chest trouble:

I cannot play sport or games……………………………………

T F

I cannot go out for entertainment or recreation………………

T F

I cannot go out of the house to do the shopping……………

T F

I cannot do housework…………………………………………

T F

I cannot move far from my bed or chair……………………

T F

Here is a list of other activities that your chest trouble may prevent you doing: (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect).

• going for walks or walking the dog
• sexual intercourse
• going out to church, or place of entertainment
• going out in bad weather or into smoky rooms
• visiting family or friends or playing with children

Please write in any important activities (such as those above or others) that your chest trouble may stop you doing:

…………………………………………………………………………………………

…………………………………………………………………………………………

Now, would you mark the bracket below (only one) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do…………

T

It stops me doing one or two things I would like to do…………

T

It stops me doing most of the things I would like to do…………

T

It stops me doing everything I would like to do……………..

T

V1 November 2007