

**Spontaneous versus spontaneous timed mode of  
assisted ventilation in extrathoracic restrictive lung  
disease**

**Doctor of Medical Science**

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## **ABSTRACT**

Restrictive lung disease can be divided into intrathoracic restriction due to parenchymal causes and extrathoracic restriction due to chest wall disease or neuromuscular disease. Patients with extrathoracic lung restriction suffer from shortness of breath, disturbed sleep and eventually type two respiratory failure when their condition progresses.

Type two respiratory failure is characterised by hypoxaemia and hypercapnia. Effective treatment of this type of respiratory failure involves ventilatory support in the form of assisted mechanical ventilation. Non-invasive positive pressure ventilation has been a major advance in delivering mechanical ventilation since the late 1980's. This can be in the form of volume-cycled ventilation or pressure-cycled ventilation. Pressure-cycled ventilation is more commonly practised in Australia and around the world; particularly Europe; according to large multicentre surveys. This can be delivered in spontaneous mode (S) or spontaneous timed mode (ST). There is no current evidence that one mode is superior to the other, and the two modes are roughly equally practised around the world and in Australia according to the available surveys.

The aim of this research was to compare S mode to ST mode in a double-blind cross over design over six weeks in 20 patients with stable extrathoracic lung restriction from chest wall and neuromuscular disease. The study aimed to objectively assess adequacy of ventilation, quality of sleep and impact on the patient in psychomotor function, sleepiness as well as patient preference. This was assessed by performing blood gas analysis, sleep studies, psychomotor vigilance testing (PVT) as well as patient questionnaires.

We also performed a physiological arm of the study in a subset of patients, assessing the participants for ineffective efforts and poor triggering by inserting an oesophageal

balloon and monitoring for markers of effort not followed by a ventilator breath. The oesophageal balloon-catheter system was calibrated for frequency response under different conditions prior to starting this arm of the study and for adequacy of signal acquisition before each sleep study.

Due to difficulty in recruitment of participants and some patients withdrawing or failing the safety criteria for the study, a total of 13 patients completed the two arms of the study. The results of this research demonstrated that ST mode was associated with improved nocturnal oxygenation, sleep quality and fewer respiratory events than S mode in patients with stable chest wall and neuromuscular disease. There was no significant difference in daytime hypoventilation as assessed by carbon dioxide measurements.

The physiological arm of the study showed that ST mode resulted in fewer ineffective efforts than S mode, the former contributing to better sleep efficiency and correlating well with fewer respiratory events. On the other hand, the mode of ventilation had no significant effect on poor triggering of the ventilator.

The participants appeared to be less sleepy on ST than S mode; however, neither mode was associated with pathological sleepiness. There was no significant difference in patient preference between the two modes, nor was there a significant difference in psychomotor function between the modes as assessed by PVT.

In conclusion, ST mode of non-invasive positive pressure ventilation was superior to S mode in many aspects of ventilation, sleep quality and impact on the patient. Physiologically there were less ineffective efforts on ST mode, which was related to improved sleep efficiency and the frequency of respiratory events while on ventilation. The participants were less sleepy on ST than S mode, however there was no significant

difference between the two modes of non-invasive ventilation on on psychomotor function and patients did not prefer one mode over the other.

The sample size of this study was small and less than the original target, due to difficulty in recruitment and the need for participants to present to hospital on three different occasions, a considerable expectation in this relatively frail cohort of patients. The concept of measuring oesophageal pressure in awake patients was also a limiting factor in failure to achieve the target number of participants in the sub-study. This would have impacted the power of the study and the overall significance of some of the results.

Based on the results of this study, ST mode of non-invasive ventilation should be utilised rather than S mode in patients with extrathoracic lung restriction due to neuromuscular and chest wall disease. Centre specific preferences and cost need to be taken into account when implementing this recommendation. Acknowledging the difficulties with recruitment, larger (possibly multi-centre) studies of longer duration are required to determine long term health benefits such as hospital admissions and mortality in this population.

## **DECLARATION**

This is to certify that this thesis comprises only my original work towards the degree of Doctor of Medical Science. The recruitment of patients, consent to participate and organisation of the study were done by myself. In the conduction of tests, I attended all sleep studies and checked all the signals until the participant was ready to sleep on the allocated mode of ventilation. The sleep scientists then continued to observe the patient overnight and I reviewed the patient again in the morning prior to implementation of the randomised mode of ventilation. The randomisation and allocation of treatment were done by the unblinded staff member. I was solely contacted to troubleshoot any problems with the study procedures during the day or night. I personally conducted all the tests such as the psychomotor vigilance test and downloaded all the data. I also supervised all the patient questionnaires. The oesophageal balloons were all calibrated and inserted by myself. I did seek assistance from our senior scientist in the Respiratory Laboratory at Austin Health in performing the frequency response test. The calibration of each balloon was also done in conjunction with one of our scientists who also did the sleep staging and scoring. The staging and scoring of the studies were done by a blinded sleep scientist. The literature review and the writing of the whole thesis was my original work. All statistical analyses were performed by myself. All entries in the text of the thesis referring to the principal investigator refer to me.

Due acknowledgement has been made and referenced in the text to all other material used. This thesis is less than 100,000 words in length inclusive of tables, references and appendices.

**Dr Murad Ibrahim**

**July 2019**

## **ACKNOWLEDGEMENTS**

With sincere gratitude, I acknowledge all the scientific and professional help from my supervisors A/Prof Mark Howard and Prof. Christine McDonald. Their guidance, support and encouragement have been exemplary in every way. I also acknowledge the help and guidance I received from the late Prof. Robert Pierce who co-supervised this research initially until he sadly and unexpectedly passed away.

I wish also to acknowledge Austin Health and the Victorian Respiratory Support Service (VRSS) for allowing me to conduct this research at their facilities.

I wish to thank Melbourne University Medical School for allowing me to conduct and submit this original research and thesis.

I wish to acknowledge the financial assistance to this research by The Institute of Breathing And Sleep (IBAS) and the Austin Hospital Medical Research Council (AHMRC).

I wish to thank A/Prof Fergal O'Donoghue, Prof David Berlowitz, Mr Peter Rochford, Mr Chris Smith, Ms Nicole Sheers, Mr Tom Churchward, Mr Warren Ruehland, Mr Daniel Stadler and our other physiotherapists and sleep scientists who provided support throughout the research project.

I wish to thank all the participants in this research project who gave up their time and effort to help conduct this study.

Finally, I wish to acknowledge the support of my wife, my children and the whole family, who tolerated long hours of continuous work and not being available with them.

I wish to particularly acknowledge the support and encouragement of my late father Dr G Ibrahim and my late mother Alice who always gave me encouragement and moral support.

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**List of abbreviations:**

PaO<sub>2</sub>: Arterial O<sub>2</sub>

SpO<sub>2</sub>: O<sub>2</sub> saturation by pulse oximetry

PaCO<sub>2</sub>: Arterial CO<sub>2</sub>

IPAP: Inspiratory Positive Airway Pressure

EPAP: Expiratory Positive Airway Pressure

TiMin: Minimum Inspiratory Time

TiMax: Maximum Inspiratory Time

NMD: Neuromuscular Disease

CWD: Chest Wall Disease

REM: Rapid Eye Movement Sleep

NREM: Non-Rapid Eye Movement Sleep

HMV: Home Mechanical Ventilation

PCV: Pressure Controlled Ventilation

VCV: Volume Controlled Ventilation

NIV: Non-Invasive Ventilation

AHI: Apnoea Hypopnoea Index

OAI: Obstructive Apnoea Index

MAI: Mixed Apnoea Index

CAI: Central Apnoea Index

PVT: Psychomotor Vigilance Test

d-EMG: Diaphragm EMG

sc-EMG: Scalene EMG

Poes: Oesophageal pressure

FVC: Forced Vital Capacity

FEV1: Forced Expiratory Volume in one second

FER: Forced Expiratory Ration

TLC: Total Lung Capacity

FRC: Functional Residual Capacity

ERV: Expiratory Reserve Volume

CO: Carbon Monoxide

DLCO: Diffusion Capacity of Carbon Monoxide

CT: Total Lung Compliance

CL: Lung Compliance

CCW: Chest Wall Compliance

FEF: Forced Expiratory Flow

Pdi: Transdiaphragmatic pressure

MIP: Maximum Inspiratory Pressure

MEP: Maximum Expiratory Pressure

SNIP: Stiff Nasal Inspiratory Pressure

# **Chapter 1: Background & Literature Review**

## **1.1 Introduction**

Restrictive lung disease comprises a group of conditions characterised by reduced lung capacity which may lead to shortness of breath, and when severe, respiratory failure. Causes of restrictive lung disease may be intrathoracic or extrathoracic. Intrathoracic causes reflect parenchymal lung disease, while extrathoracic causes are due to muscle weakness, obesity or structural abnormalities in the chest outside the lungs.

While the lungs themselves are generally healthy in extrathoracic lung restriction, shortness of breath may develop as a consequence of the increased work of breathing required to expand the stiff chest wall and/or weak respiratory muscles. Eventually, respiratory failure can develop as the fatigued muscles fail to maintain this high level of work of breathing for long periods. The condition is worse during sleep and when lying in the supine position, due to central inhibition of respiration and the increased mechanical load on the inspiratory muscles with reduction in functional residual capacity (FRC).

As a result, patients with extrathoracic lung restriction may need assistance to maintain normal or close to normal ventilation, particularly during sleep or in the recumbent position. This form of long term ventilatory support is called assisted ventilation. Assisted ventilation can be provided as invasive ventilation, where intubation of the airway via endotracheal tube or tracheostomy is required, or as non-invasive ventilation (NIV) which delivers ventilatory support via a face mask. The latter option is generally preferred due to the many challenges associated with the insertion and care of a tracheostomy. There are many potential complications associated with tracheostomies including early and late complications; some of which can be life-threatening. Initially after insertion, bleeding, acute infection, acute obstruction and dislodgement are

possible causes of early complications. Late complications can include the formation of granulation tissue, development of tracheomalacia, fistula formation and tracheal or subglottic stenosis [1]. In addition, phonation through a tracheostomy tube can be challenging and requires training for the carer and the patient. With severe muscle weakness and respiratory failure, phonation through a tracheostomy tube may not be even possible. There is often a multidisciplinary team consisting of a nurse, a speech pathologist, and a physician involved in the patient's tracheostomy care [2]. On the other hand, non-invasive ventilation is associated with fewer complications and allows easier transition into the home environment once established.

This research evaluated the impact of two common forms of non-invasive assisted ventilation "Spontaneous Mode" and "Spontaneous Timed Mode" on ventilation, sleep quality, patient comfort and psychomotor effects.

## **1.2 Control of breathing**

Control of breathing is a complex and interactive process that involves many of the body systems. It is largely automated and intrinsic; hence its descriptor "involuntary respiration"; that is respiration controlled by the brain stem. However, there is also higher control in the cerebral cortex, which can control and override this process, and is described "voluntary respiration".

The main respiratory centre lies in the medulla, where inspiration and expiration are controlled by groups of nuclei in two separate areas. The "dorsal group" is responsible for initiating inspiration, while the "ventral group" is responsible for expiration. Whilst these centres control normal respiration, input from other centres such as the "pneumotaxic centre" in the pons, can modify the depth and rate of respiration. Other centres that can influence ventilation include the limbic system and the thalamus. All

these centres together are identified as the “central controller” part of the respiratory system [3].

Impulses from the central controller stimulate the effector respiratory muscles to implement the process of ventilation. The respiratory muscles are comprised of upper airway muscles, inspiratory muscles and expiratory muscles. The upper airway muscles are responsible for maintaining patency of the upper airway and assist in coughing. These include the vocal cords abductor muscles, dilators of the nares, elevators of the palate, dilators of the pharynx, and retractors of the tongue. The last three are particularly important in maintaining the patency of the upper airway during sleep.

The dilators of the upper airway are of particular interest and have been studied extensively in the literature addressing pathophysiology of sleep disordered breathing [4-6]. They can be divided into phasic muscles, which activate more during inspiration than expiration, and tonic muscles, which have the same level of activity during inspiration and expiration. The two main dilators of the airway are the genioglossus and tensor palatini muscles. The genioglossus acts as an inspiratory phasic pattern muscle as well as a tonic pattern muscle, whilst the tensor palatini is a purely tonic muscle. The pharyngeal dilator muscles receive three neural inputs. The first is via the mechanoreceptors in the upper airway which are stimulated by negative pressure reflexes. This, in turn, stimulates an afferent response from the superior laryngeal nerve followed by an efferent response from the hypoglossal nerve to the genioglossus muscle. The second input comes from the respiratory neuronal centre in the medulla unrelated to the mechanoreceptors in the airway. The third input comes from the wakefulness stimulus to maintain arousal via adrenergic and serotonergic neurones and have a tonic excitatory effect on the motor neurones in the hypoglossal nerve that stimulates the pharyngeal dilator muscles [7, 8]. Failure to maintain appropriate activity

in the pharyngeal dilator muscles to oppose the effects of the collapsing forces of tissues surrounding the upper airway and the negative pressure created by the diaphragm results in sleep disordered breathing, manifesting as obstructive sleep apnoea and occasionally as nocturnal hypoventilation [7, 9].

The inspiratory muscles are mainly formed of the diaphragm muscle, the parasternal intercostal muscles, the scalene muscles of the neck, the sternomastoids, trapezius, serratus and lateral external intercostal muscles. The diaphragm is innervated by the phrenic nerves which derive their innervations from the cervical spinal cord from levels C3 to C5. The diaphragm is responsible for 70% of the tidal volume[10].

Other inspiratory muscles are innervated at different levels in the spinal cord, but the primary inspiratory muscles are also innervated higher up in the cervical spine providing a protective mechanism against respiratory failure from spinal cord injury unless these are high in the cord. Paralysis of the intercostal muscles alone; such as occurs in low cervical spinal cord injury; causes a modest reduction in ventilatory function but does not usually lead to significant impairment in ventilation because of the effectiveness of the diaphragm.

The expiratory muscles are primarily the antero-lateral muscles of the abdominal wall including the internal and external obliques and the transversus abdominus. The lateral internal intercostals and the transversus thoracis may also aid expiratory effort. As expiration is a passive process due to elastic recoil of the chest wall, weakness of the expiratory muscles is less frequently associated with respiratory failure. The main function of the expiratory muscles is to generate force for the coughing mechanism.

The complex interactive process of control of breathing cannot be completed without an active feedback mechanism [3, 11]. This is facilitated by central and peripheral sensors called the “central chemoreceptors” and the “peripheral chemoreceptors”. The

function of a chemoreceptor is to react to changes in the chemical composition in the surrounding environment; in this case the blood and cerebrospinal fluid (CSF). The central chemoreceptors lie in the ventral aspect of the medulla, below the medullary respiratory centre and react mainly to changes in the power of hydrogen (pH). Increased hydrogen level causes acidosis and stimulates the central chemoreceptors, while a reduction in hydrogen levels inhibits these receptors. Hydrogen concentration increases when carbon dioxide (CO<sub>2</sub>) diffuses from the blood to the cerebrospinal fluid (CSF). Thus, carbon dioxide retention is the major cause of stimulus to breathing, acting through the central chemoreceptors, which in turn stimulate the central controller system to increase ventilation via the respiratory muscles in the effector system (figure 1.1). The opposite effect is true, when the resulting increased ventilation happens, as in this instance the fall in CO<sub>2</sub> inhibits the central chemoreceptors and in turn the central controller to decrease ventilation.

The peripheral chemoreceptors are located in the carotid bodies close to the bifurcation of the common carotid artery and the aortic bodies above and below the arch of the aorta. These receptors react to changes in the arterial partial pressure of oxygen (PaO<sub>2</sub>), as well as to changes in the pH and CO<sub>2</sub> levels in the blood. A reduction in PaO<sub>2</sub>, or pH or an increase in CO<sub>2</sub> levels in the blood stimulate the peripheral chemoreceptors to increase ventilation. The peripheral chemoreceptors are the main receptors that respond to hypoxaemia. They play a lesser role in response to CO<sub>2</sub> levels in the blood than do the central chemoreceptors. Peripheral chemoreceptors responding to pH are present mainly in the carotid bodies and not in the aortic bodies. In addition to the central and peripheral chemoreceptors, other receptors are present within the lungs. These include “pulmonary stretch receptors”, irritant receptors” and “J receptors”. The role of these receptors is less well understood in humans but they appear to contribute

less to the control of ventilation than do the aforementioned central and peripheral chemoreceptors [3, 10].

In summary, respiratory homeostasis relies on a complex interactive process between the controllers, the effectors and the sensors. A deficiency in any of these mechanisms can lead to loss of the normal regulation of breathing and can result in a variety of respiratory and or sleep disorders. Chronic alveolar hypoventilation leading to type two respiratory failure is one manifestation of such loss of respiratory homeostasis. Referring to the figure below (figure 1.1), the defect may involve any one or more of the arms of the triangle. The pathology may lie in the central controller such as in “primary alveolar hypoventilation syndrome”. In “carotid body dysfunction”, the problem lies within the sensor. Where there is muscle weakness; such as in neuromuscular disease; or mechanical disadvantage of the respiratory muscles; such as in chest wall disease and obesity; the defect lies in the effectors [10].

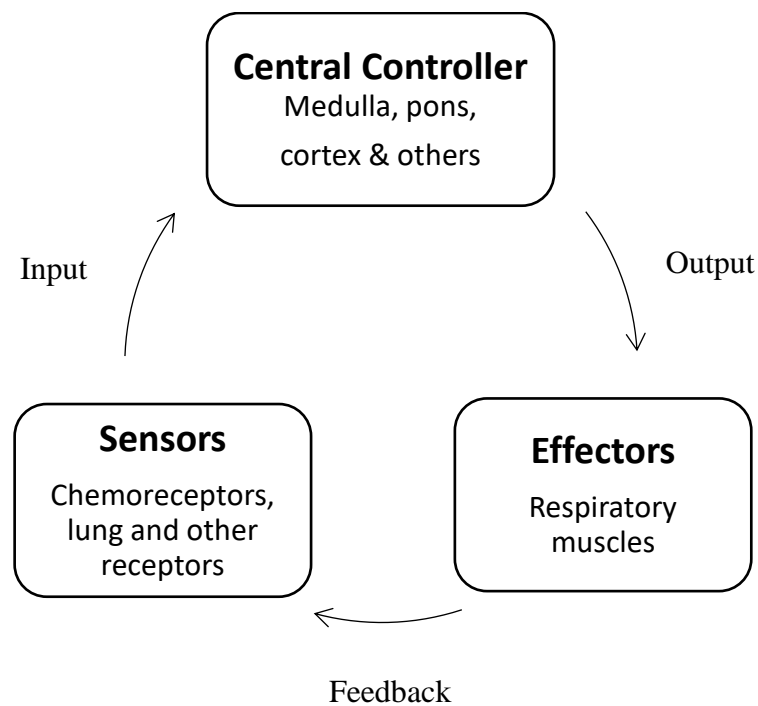


Figure 1.1 Control of ventilation

### **1.3 Lung mechanics**

Inspiration is an active process involving a number of muscles with the key muscle involved being the diaphragm [12, 13]. When the diaphragm contracts the abdominal contents are forced down and forward with vertical elongation of the thoracic cavity. The rib margins are lifted and moved outwards leading to an increased transverse diameter of the chest[14]. Contraction of the external intercostal muscles causes the ribs to move upward and forward leading to chest expansion laterally and antero-posteriorly[15]. The combination of all these actions results in the development of negative pressure within the thoracic cavity that expands the lungs.

Expiration, on the other hand, is a passive process during quiet breathing. This is due to the elastic recoil of the lungs and chest wall returning the chest to its equilibrium position. On the other hand, during exercise, the process becomes active with contraction of the expiratory muscles particularly the muscles of the abdominal wall, and to a lesser extent the internal intercostal muscles [3, 10].

Work of breathing is defined as the product of pressure and volume per breath. In other words, it is the amount of work required to overcome the tendency of the lungs to collapse as well as to displace the chest wall and abdomen to allow expansion of the lungs. Factors that affect the work of breathing include lung elasticity, upper and lower airway resistance and chest wall compliance. For example, in intrinsic restrictive lung disease, the work of breathing is increased due to decreased elasticity of the lungs. On the other hand, the work of breathing is increased in obstructive lung disease due to increased lower airway resistance [16]. In chest wall disease, the work of breathing is increased due to reduced chest wall compliance from the stiffness of the chest wall, and anatomical malalignment of the thoracic cage and spine [10].

Compliance is defined as the change in volume per unit pressure change. Total lung compliance ( $C_T$ ) is the sum of lung compliance ( $C_L$ ) and chest wall compliance ( $C_{CW}$ ). The total lung compliance has a value of 200ml/ cm H<sub>2</sub>O, but there is a range of factors that can affect it. The lungs are normally very compliant estimated to be 150ml/ cm H<sub>2</sub>O. Lung compliance is defined as the change in lung volume per unit change in transmural pressure gradient between the alveolus and pleural space [17]. Lung compliance ( $C_L$ ) is reduced with any increase in fibrous tissue in the lung (pulmonary fibrosis). It can also decrease in the presence of alveolar oedema and pulmonary venous congestion due to engorgement of the lung with either fluid or blood. If the lungs are under-ventilated for a long time, compliance is also reduced due to atelectasis or collapse of some segments of the lung. When parts of the lungs are partially collapsed, surface tension increases, making it more difficult for the lung to inflate; and hence reducing compliance. Compliance increases with ageing due to an increase in the elastic properties of the lung tissue[3]. Chest wall compliance ( $C_{CW}$ ) is defined as the change in lung volume per unit change in the pressure gradient between the atmosphere and the intrapleural pressure. Its value is also estimated at 200 ml /cm H<sub>2</sub>O. Chest wall compliance is determined by the elastic properties of the thoracic cage, which comprises the ribcage and the diaphragm. The thoracic cage has the tendency to bow out, which helps maintain lung inflation[3, 10, 18, 19]; however, this may change with extra-thoracic restrictive diseases. Factors that can reduce chest wall compliance include obesity, kyphoscoliosis and even pathological skin conditions such as chronic severe scarring [17, 20]. Chest wall compliance can be also reduced in adults with chronic neuromuscular disease due to stiffening of the chest wall from the chronic reduction in chest wall motion from muscle weakness [21, 22].

Simply put, the equilibrium volume of the lung or functional residual capacity occurs when the elastic recoil of the lung is balanced by the tendency of the chest wall to spring out.

Pleural pressure is the pressure in the pleural space surrounding the lungs. This is the space between the pleural membrane that surrounds the lungs, the so-called “visceral pleura” and the pleural membrane that lines the inside of the chest wall, the so-called “parietal pleura”. The pleural space normally contains a few millilitres of pleural fluid and the pressure inside the pleural space is normally sub-atmospheric (i.e. negative) in order to help maintain the lung in an inflated position. The pressure in the pleural space is not uniform as a consequence of the effect of gravity. It is generally less negative in the dependent areas of the lung, that is less negative in the lung bases than the apex in the upright position and less negative posteriorly than anteriorly when lying supine.

The alveolar pressure is the pressure inside the alveoli and equals the atmospheric pressure or zero at rest. It is negative during inspiration allowing air to flow from the higher pressure at the mouth down through the airways into the alveoli. Alveolar pressure becomes positive during expiration to allow air to flow out from the lungs into the atmosphere.

The size of the lung is determined by the balanced forces of the alveolar pressure and the pleural pressure or what is referred to as the “trans-pulmonary pressure”. Given that the alveolar pressure is generally uniform in the lung, the apices tend to be more inflated than the lung bases due to the more negative pressure in the pleural space there.

## **1.4 Effect of sleep and posture on respiratory function and ventilation**

### **1.4.1 Effect of sleep**

Sleep is an important part of our daily routine, accounting for approximately 30% of our human lives. Originally thought to be a completely inactive phase of our life, positron emission tomography (PET) studies have demonstrated that our brains are rather active during sleep, particularly during rapid eye movement sleep (REM) or dreaming [23]. Whilst the mechanisms are not fully understood, sleep helps us rejuvenate, repair our body tissues and consolidate our memory [24, 25]. For example, growth hormone is secreted in large amounts during sleep and this promotes growth [26].

There are a number of physiological changes that happen during sleep affecting all body systems in an integrated fashion. Body systems involved include the somatic nervous system, autonomic nervous system, cardiovascular system, metabolic and endocrine system, gastrointestinal tract and respiratory system. The physiological changes in the respiratory system during sleep occur to match the reduced metabolic state. The neural drive to stimulate breathing is reduced when compared to wakefulness [11, 27]. In general, there is a reduction in ventilation including in parameters such as minute ventilation, tidal volume and respiratory rate. The reduction is more pronounced in REM rather than non-rapid eye movement sleep NREM sleep [28]. The partial pressure of carbon dioxide in the blood normally rise during sleep by 2-7 mmHg [10]. There is a reduction in respiratory muscle tone; particularly during REM sleep; including in the tongue, pharyngeal muscles, laryngeal muscles and the intercostal muscles. As a result of this reduction in muscle tone particularly in the intercostal muscles, and the disadvantage of the diaphragm positioning in the recumbent position, the functional

residual capacity is reduced during sleep even in healthy individuals [29]. The sensitivity and reflexes of the upper airway are also reduced during sleep [30] while the airway resistance increases, which promotes obstruction in patients with obstructive sleep apnoea (OSA)[31]. There is a reduction in the wakefulness stimulus to the upper airway muscles mainly the genioglossus and the tensor palatini muscles, the two main dilators of the upper airway. As a result, the balance of forces between upper airway dilator muscles, that maintain patency of the upper airway, and the collapsing forces created by the intraluminal negative pressure, generated by the diaphragm and the extraluminal pressure from tissues surrounding the airway, is lost and the upper airway tends to collapse [7].

The chemosensitivity of the respiratory receptors is also affected by sleep. The result is blunting of both hypercapnic and hypoxic ventilatory responses [32].

As sleep is not homogeneous, these changes in the range of parameters mentioned vary depending on the phase of sleep we are in [11]. During NREM sleep, breathing is somewhat unstable, particularly during the first and second stages of NREM sleep (known as N1 and N2, respectively). On the other hand, in the third stage (N3) or what is known as slow wave sleep, respiration becomes more stable. During REM sleep (R), however, ventilation becomes unstable and variable ranging from being decreased, the same or increased when compared to NREM sleep or wakefulness [9, 24].

Although the above-mentioned observed physiological changes occurring during sleep appear not to impact healthy individuals significantly, blunted hypoxic and hypercapnic ventilatory responses in the presence of weak respiratory muscles and/or increased work of breathing, can lead to hypoventilation in patients with respiratory and neuromuscular disease [24, 31-33].

For example, during REM sleep, there is reduced muscle tone in the intercostal muscles and effective ventilation relies mainly on diaphragm function. In conditions where the diaphragm has been affected by weakness, such as in motor neurone disease or poliomyelitis, severe hypoventilation can develop [33]. In addition to the changes in control of breathing, there is also a mechanical disadvantage when the individual lies horizontal during sleep as discussed in the following section.

#### **1.4.2 Effect of posture on respiratory vital capacity and diaphragm function**

In healthy individuals, changing position from upright to supine has little effect on respiratory function and ventilation, with the vital capacity (VC) estimated to fall by less than 10% [34, 35]. On the other hand, patients with neuromuscular disease can have a significant fall in their VC in the recumbent position. A fall of 30% or more indicates severe diaphragm muscle weakness [10, 36].

In a study by Chen et al. [37], 33 patients with neuromuscular disease were assessed for percentage change in forced vital capacity (FVC) and forced expiratory flow (FEF) when changing from a seated to a supine position. Just over half of these patients were spontaneously breathing and the rest were receiving non-invasive ventilation. There was a significant 14-fold percentage change in FVC (%FVC) in patients on non-invasive ventilation when compared to spontaneously breathing patients. There was no significant change in forced expiratory flow. The study suggested that those who needed non-invasive were more likely to have a postural fall in vital capacity than those who were still spontaneously breathing. Whilst this association between the percentage change in FVC and being on non-invasive ventilation is not predictive of the need for initiating

ventilation, the authors rightly concluded that more longitudinal studies are required to assess this relationship [37].

In another study conducted over two years, Fromageot et al. assessed diaphragm function in sitting and supine position in 24 patients with generalised neuromuscular disease from various causes. Vital capacity (VC), forced expiratory volume in one second (FEV1), total lung capacity (TLC) and transdiaphragmatic pressure (Pdi) were measured. Patients with paradoxical diaphragmatic movement had lower lung volumes including TLC, VC and FEV1 than patients with non-paradoxical diaphragmatic movement. Similarly, there was a significantly larger drop in all these values in the supine position when compared to sitting position [38].

Based on this concept, measurement of sitting and supine vital capacity has become standard practice in specialised centres looking after neuromuscular disease patients.

## **1.5 Lung function tests in restrictive lung disease**

Pulmonary function testing in lung restriction concentrates on measurement of lung volumes through spirometry and body plethysmography as well as specialised tests to assess respiratory muscle function. Spirometry and lung volume measurements characteristically show reduced total lung capacity, vital capacity, residual volume and functional residual capacity. Respiratory muscle strength testing such as maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) may reveal reduced pressures in the case of neuromuscular disorders. The sniff nasal inspiratory pressure (SNIP) may also be reduced and is a marker of diaphragm muscle weakness. Gas transfer, although often not measured after diagnosis, is reduced and usually corrects for alveolar volume in extrathoracic restriction.

Pulmonary function testing involves a number of manoeuvres that measure airflow, lung volumes, gas transfer and respiratory muscle strength. A simple and essential test is spirometry, which typically includes the FVC and the FEV1. From these two measurements, the forced expiratory ratio (FER) is calculated. These measurements are referred to as dynamic lung volumes. In restrictive lung disease, the typical pattern shows a normal or increased FER, with reduction in FVC and FEV1. A poor effort or a coexisting airflow obstruction can result in a falsely reduced FVC. In the case of the latter, a slow vital capacity (SVC) is measured but may still show a falsely low result. The ultimate test in both situations is the measurement of static lung volumes usually by body plethysmography (body box) as the gold standard although it can be measured in other ways. The body box method is based on Boyle's law which states that for any given mass of gas, the product of pressure and volume remains constant provided the temperature doesn't change. It involves the patient panting against a shutter valve in a mouthpiece inside the closed box. By measuring the pressure from the mouthpiece and comparing it to the known pressure and volume inside the box, the volume of air on the lungs can be calculated. Different manoeuvres are done to calculate different lung volumes. The values obtained include the TLC, the FRC, and the residual volume (RV)[39]. Typically, in restrictive lung disease, the TLC is reduced due to reduced lung compliance in intrinsic lung disease and chest wall compliance in extrathoracic lung disease. The FRC and RV may be reduced in restrictive lung disease; particularly parenchymal lung disease (e.g. pulmonary fibrosis); but may be normal in chest wall and neuromuscular disease. This is due to the fact that expiratory muscle weakness (intercostal and abdominal muscles) in these conditions limits full expiration and the ability to achieve maximal exhalation. Air remains in the lungs and causes the normal or even increased residual volume (RV) and normal FRC [40-42].

Checking lying and standing vital capacity is important in picking up early weakness in diaphragm function as covered earlier in the section on the effect of posture on lung function.

Other forms of lung function testing include measurement of gas transfer. This is usually done by measuring the diffusion capacity of carbon monoxide (CO) in the lungs (DLCO). CO has physical properties similar to oxygen when diffusing from the alveolar membranes of the lungs into the bloodstream via the pulmonary capillaries. The measurement is usually corrected for the alveolar volume (VA) to correct for areas in the lung that are not aerated (Krogh constant) and is referred to as KCO or DLCO/VA. In restrictive lung disease due to a pulmonary parenchymal problem the DLCO and KCO are typically reduced; however, if lung restriction is due to an extra-thoracic factor such as in chest wall disease or neuromuscular disease the DLCO may be reduced but corrects when adjusted for the alveolar volume (i.e. normal or elevated KCO). With the latter, the relationship is not very linear and generally the KCO needs to be interpreted only in the context of DLCO.

Another form of lung function testing that is relevant to our cohort of patients with restrictive lung disease secondary to extra-thoracic problems is the measurement of respiratory muscle strength. This can be done by measuring the pressure generated by inspiring and expiring against a closed airway at the mouth. The maximal inspiratory pressure and maximal expiratory pressure are usually measured and generally correlate to the degree of neuromuscular weakness; however, they can be reduced in other conditions such as chest wall disease and have a wide range in value making interpretation difficult at times. Mastery of the technique by the patient and even the respiratory scientist to produce maximal effort can be difficult and inaccurately low measurements to submaximal effort can be encountered. A normal test for maximal

pressures usually precludes the diagnosis of muscle weakness [43] The sniff nasal inspiratory pressure is an alternative and complementary test to measure the inspiratory muscle strength. It is generally easier to perform than the MIP particularly in patients with neuromuscular disease who cannot obtain a good mouth seal [44].

## **1.6 Types of Restrictive lung disease**

Restrictive lung disease can be divided into intrathoracic causes; such as interstitial lung disease; and extrathoracic causes, which is the main type of restriction that will be discussed in this thesis. Extrathoracic causes include diseases associated with neuromuscular weakness such as various types of myopathy, neuropathy or muscular dystrophy. In this circumstance reduced respiratory muscle strength may result in an inability to match the required work of breathing, resulting in inadequate minute ventilation. Other extrathoracic conditions include chest wall disease such as kyphoscoliosis or severe chronic pleural thickening. Obesity has also emerged as an important cause of extrathoracic lung restriction in the last few decades. In all these causes of extrathoracic restriction, reduced chest wall compliance increases the work of breathing and when this is severe the respiratory drive and muscles are unable to match the required increased work, resulting in inadequate minute ventilation. When such decompensation occurs, intrathoracic causes of restriction are usually associated with type I respiratory failure, which is characterised by hypoxaemia ( $\text{PaO}_2 < 60$  mmHg) but no hypercapnia. This is postulated to be due to the fact that intrathoracic lung disease is associated with hyperventilation with low tidal volumes and high respiratory rate, rather than hypoventilation[45]. On the other hand, decompensation from extrathoracic lung restriction causes type II respiratory failure characterised by

both hypoxaemia ( $\text{PaO}_2 < 60 \text{ mmHg}$ ) and hypercapnia ( $\text{PaCO}_2 > 45 \text{ mmHg}$ ) or what is often described as hypoventilation.

This thesis deals with type II respiratory failure (or hypoventilation) due to extrathoracic disorders such as kyphoscoliosis and neuromuscular diseases but not obesity. Treatment of this type of respiratory failure includes providing supportive mechanical ventilation to compensate for the patient's inability to maintain the required minute ventilation.

## **1.7 Conditions associated with extrathoracic restrictive lung disease**

Most neuromuscular diseases can cause lung restriction due to involvement of the respiratory muscles as described above. Common conditions associated with extrathoracic restriction and type II respiratory failure will be discussed here.

### **1.7.1 Neuromuscular Disease**

One of the commonest causes of significant lung restriction is motor neurone disease (MND), a condition which affects both upper and lower motor neurones. It can involve both the chest wall respiratory muscles; such as the intercostal muscles; and the diaphragm leading to progressive shortness of breath and eventually type II respiratory failure, including hypoxaemia and carbon dioxide  $\text{CO}_2$  retention. Bulbar dysfunction is also common in a subset of patients and leads to impaired speech and swallowing. The weakness of the abdominal muscles together with bulbar dysfunction leads to impaired cough reflex adding further risks of sputum retention and aspiration.

Gastrostomy tubes are often required to improve quality of life and facilitate nutrition.

The disease is usually progressive with 90% mortality within 5 years from diagnosis.

[46] Non-invasive ventilation has been shown to improve survival in patients with

motor neurone disease without severe bulbar dysfunction. The only randomised controlled study allocated 41 patients with motor neurone disease to either non-invasive ventilation or standard care. Pressure support ventilation was initiated using a Resmed VPAP STII in ST mode. A variety of interfaces were used including nasal masks, oro-nasal masks, full face masks and mouthpiece, the latter used mainly in patients with poor upper limb function but preserved bulbar function. There was a median survival benefit of 205 days in the ventilated group in comparison with the standard care group. Quality of life was also assessed and there was more sustained improved quality of life in the ventilated group than in the standard of care group. The benefits on survival and quality of life were seen in the patients with normal bulbar function and moderate bulbar dysfunction but not in those with severe bulbar dysfunction ones[47]. On the other hand, a recent study assessed 1198 patients with motor neurone disease identified through a large clinic database. The patients were phenotyped according to their clinical presentation. The study aimed to determine the effect of non-invasive ventilation on the rate of decline in pulmonary function as well as survival in patients who were implemented on NIV versus those did not receive ventilation. The results of the study indicated that there was a survival benefit in patients with bulbar disease and amyotrophic lateral sclerosis (ALS)-lumbar but not in those patients with flail limb and ALS-cervical. The rate of decline in lung function improved in all subtypes. The study was a retrospective analysis rather than a randomised study but with the benefit of having a large number of patients in comparison to the small number in the only randomised study described above. The authors argued that it was unethical to consider doing another randomised controlled study on patients with motor neurone disease to assess the effect of non-invasive ventilation given the evidence already established by the randomised study[48].

In a retrospective analysis of 179 patients with amyotrophic lateral sclerosis (ALS), Georges et al. assessed for the presence of upper airway obstruction while on non-invasive ventilation and the impact on prognosis and survival. The ventilator settings were adjusted however some patients had some residual events even after adjustments were made. The patients who were inadequately treated with non-invasive ventilation despite adjustment of the ventilator (28 patients), as well as those with obstructive events without a drop in oxygen saturation, who did not require adjustment in ventilation settings (38 patients), had shorter survival. The authors concluded that the presence of upper airway obstruction in patients with amyotrophic lateral sclerosis while on non-invasive ventilation was associated with poor prognosis [49]. Although the study was an observational one and needs to be interpreted in this context, it highlights the importance of optimising ventilation and avoiding residual respiratory events as a goal of therapy.

Different types of muscular dystrophy can cause respiratory muscle involvement leading to lung restriction and respiratory failure. This is more commonly seen early in Duchenne and Becker muscular dystrophies and later in life in limb-girdle, facioscapulohumeral and myotonic muscular dystrophy. A mutation in the dystrophin gene; that is present in different locations depending on the subtype of muscular dystrophy; is responsible for these forms of myopathy. It causes a change in the structure of the body muscles inducing replacement of the muscular tissue with connective tissue and fat. Although disease onset in the muscular dystrophies usually starts early in life, the trajectory of muscular dystrophies is slower than seen in MND; with a mean survival in the Duchenne subtype of 27 years. With multidisciplinary management including non-invasive ventilation, these patients can now increasingly survive longer into adult life. [50, 51]. Other symptoms apart from the respiratory

complications already mentioned, depend on the type of muscular dystrophy. Similar to motor neurone disease modern standards of care require attention to every aspect including physiotherapy, vaccinations, nutritional care and mechanical ventilation[52]. Glucocorticoids are the main form of pharmacological treatment for Duchenne Muscular Dystrophy starting from the age of four years old. Recent systematic reviews and practice guidelines concluded that corticosteroids are effective in improving strength and pulmonary function and should be offered to children[53-55]. Non-invasive ventilation is an integral part of the management of patients with Duchenne muscular dystrophy. In one study ten patients with Duchenne muscular dystrophy with a mean age of  $20.1 \pm 5.2$  years, were randomised to either non-invasive ventilation or simple conservative management, five in each arm of the study. The ventilated patients were on volume cycled ventilation via a Puritan-Bennett portable ventilator through two nasal armed cannulas supported by a custom-made nasal interface fitted to the face. There was a higher survival rate in the ventilated group than in the conservative management group. There was also less loss of ventilatory function in the ventilated group than in the conservative management group [56]. Another study by Simonds et al. showed improved survival in patients with Duchenne muscular dystrophy who have developed type II respiratory failure when treated with non-invasive ventilation when compared to historical standard survival rates of 9.7 months. This study was not randomised as the investigators felt it was unethical to deny these patients non-invasive ventilation. Twenty-three patients were implemented on non-invasive ventilation and followed up for seven years. All patients were on assist control mode through a nasal interface with twenty on pressure support ventilation and three on volume cycled ventilation. The first-year survival was 85% and two-year survival was 73% and was maintained at five years. The authors concluded that non-invasive ventilation is likely

to increase survival in patients with Duchenne muscular dystrophy who have type II respiratory failure[57].

In another study by Ishikawa et al. 187 patients with Duchenne muscular dystrophy were followed up from the year 1964 onwards. The patients were divided into three groups which had a chronological sequence. Group one, who were followed up until 1984, received supplemental oxygen only. Group two, who were followed up from 1984 until 1991, received oxygen in addition to a tracheotomy. They were managed by lung recruitment manoeuvres including air stacking and deep lung insufflation. Group three was managed with non-invasive ventilation through volume cycled ventilators except for two patients who were switch to pressure cycled mode due to aerophagia. They also received mechanically assisted coughing as well as cardioprotective medications (in the presence of cardiomyopathy) from 1991 onwards. A Kaplan-Meier analysis showed improved survival by approximately ten years between the three groups, with the lowest being group one and the highest group three [58]. Although the studies are somewhat limited, there is quite a strong signal that non-invasive ventilation prolongs survival in Duchenne muscular dystrophy, as concluded in the most recent meta-analysis [59].

Non-invasive ventilation via a nasal mask, full face mask or mouth-piece is preferred to invasive methods which are usually delivered via tracheostomy. As mentioned previously, invasive ventilation is associated with more complications such as respiratory and skin infections, blockage of the internal lumen due to inspissated secretions as well as recurrent formation of granulation tissue around the tracheostomy site. It also requires extra care due to the need for frequent suctioning on a daily basis and change of tracheostomy tube every few months.

### **1.7.2 Chest wall disease**

The other main type of extra-thoracic restriction is chest wall disease, common causes of which are obesity, kyphoscoliosis, ankylosing spondylitis, pectus excavatum and post thoracoplasty. The latter was a common procedure during the 1940s and 1950s to treat pulmonary tuberculosis and still occurs, on occasion, to the present day [10].

Due to the stiff chest wall and reduced compliance, associated with these conditions the respiratory muscles are fatigued and unable to sustain the increased work of breathing. The respiratory muscles and the diaphragm are at a mechanical disadvantage which impairs their mobility. With time the diaphragm position is altered which further impairs diaphragmatic function [60]. There is good evidence to support the use of non-invasive ventilation in restrictive lung disease from chest wall disease. One study reported benefits in daytime hypercapnia, respiratory muscle strength and quality of sleep [61].

Another important cause of chest wall disease is the post-polio syndrome. The disease is caused by oral infection with an enterovirus that spreads into the nervous system causing either bulbar, bulbospinal or spinal poliomyelitis. In the spinal cord, poliomyelitis affects the motor neurons in the anterior horn cells leading to lower motor neurone paralysis. Sensation is not affected. Post-polio syndrome is defined as the development of new neuromuscular symptoms at least 15 years after the acute paralytic episode. There is progressive deterioration in motor neuronal function which starts to occur after 20 years from the original illness. The term post poliomyelitis progressive muscular atrophy (PPMA) is also often used to describe the same phenomenon [62]. There are a number of hypotheses offered to explain the mechanism of ongoing denervation that happens after the initial infection and continues on for years. These include stress and overuse of motor neurons, persistent viral infection, ageing and

immunological mechanisms [63]. The average time for the development of post-polio syndrome is about 30 years and is estimated to occur in nearly 30% of patients who were affected by paralytic polio [64]. The post-polio syndrome can lead to respiratory failure due to lung restriction from kyphoscoliosis and or diaphragm and respiratory muscle weakness. In a study where 209 patients with poliomyelitis were followed up for years, Howard et al. highlighted that respiratory failure and nocturnal hypoventilation were associated with late progressive scoliosis [65]. The management of the sequelae of post-polio syndrome requires a multidisciplinary approach and usually involves orthopaedic operations to correct spinal deformities, orthotic fittings, physiotherapy and pacing techniques as well as other respiratory support [66]. Ventilation is an important part of the management plan when evidence of hypoventilation exists. [67] During the polio epidemic in the first half of the 20th century, negative pressure ventilation mostly through iron lungs was widely used for patients with respiratory compromise. With the advent of positive pressure ventilation, treatment of respiratory failure secondary to polio became easier and more feasible. Updated Cochrane reviews found consistent evidence of benefit from non-invasive ventilation in chronic alveolar hypoventilation secondary to central nervous system disorders, neuromuscular and chest wall disease [59, 68, 69]. In the most recent version of the Cochrane review [59], 10 trials were included with 173 participants in total. Different modes of ventilation were used including volume cycled, pressure cycled and bilevel positive airway pressure (BiPAP). Four trials assessed mortality as an outcome. The review concluded that there was therapeutic benefit in alleviating symptoms of chronic hypoventilation as well as reduced unplanned admission to hospital. Survival benefit was evident in motor neurone disease and Duchenne muscular dystrophy due to the natural short survival history [47, 56], while this was more difficult to demonstrate

in conditions with longer life expectancy and rarer conditions. The authors commented that although the level of evidence was considered low, there was a consistent benefit as described above and that larger and more long-term studies are required to establish long-term benefits and cost-effectiveness.

### **1.7.3 Obesity**

Obesity, defined as a body mass index (BMI) of  $> 30$  kg/metre squared, has emerged as a major health risk in the last few decades. It has been linked to a number of significant complications affecting various body systems including the metabolic system causing insulin resistance, the cardiovascular systems causing pulmonary hypertension and increased cancer risk [70-72]. Obese patients are at a higher anaesthetic risk and adequate precautions and planning are required perioperatively including the possible need for care in the intensive care unit (ICU) [73].

The respiratory system is also significantly impacted by the effects of chronic obesity[74]. Morbid obesity is associated with chronic and often severe asthma [75]. It is also linked to extrathoracic lung restriction and type II respiratory failure. The latter is referred to as “obesity hypoventilation syndrome” (OHS) in contrast to simple obesity which does not result in type II respiratory failure.

The definition of OHS entails the development of hypercapnia ( $\text{PaCO}_2 > 45$  mmHg) in an obese patient with sleep disordered breathing, where no other cause for the rise in  $\text{CO}_2$  can be found [76]. The condition is relatively common in patients with a BMI  $> 35$  kg/metre squared, which was found to be 31% in one series with an increasing frequency in severely obese patients with a BMI  $> 50$ , at 48% [77]. The mechanism of hypercapnia in obesity hypoventilation syndrome is complex and reflects the overall impairment of compensatory ventilatory mechanisms in maintaining normal  $\text{CO}_2$

levels. This impairment is due to the complex interaction between the high BMI, the respiratory drive, the presence of sleep disordered breathing and activity of adipokines (such as leptins) [78]. Obesity causes impairment of lung function in a number of ways. The main abnormality when measuring spirometry and lung volumes is that of a restrictive pattern namely reduction in both FEV1 and FVC. Obesity also causes a reduction in both FRC and expiratory reserve volume (ERV) due to reduced chest wall compliance as the increase in adipose tissue compresses the rib cage and abdomen leading to reduced elastic recoil of the chest wall [79, 80]. The reduction in ERV leads to small airway closure and air trapping. This result in expiratory flow limitation and the development of intrinsic positive end-expiratory pressure (PEEPi), which is accentuated by supine position during sleep. As a result, the work of breathing is higher in these patients [81]. Other work has also shown evidence of increases in airway resistance and respiratory resistance when these have been studied across a spectrum of different BMIs ranging from mild to severe morbid obesity [82]. The above impairments in lung function in those with significantly increased BMI, lead to an increase in the work of breathing. When this was studied by Sharp et al., the impairment in lung function in obese patients (defined as weights from 115-168 kg) was found to be triple that of normal subjects (defined as weights from 62-94 kg) [83]. The effects of obesity on lung function are related to the morphologic pattern of adipose tissue distribution with central patterns being more impactful on lung function than peripheral patterns of distribution as measured by waist-to-hip ratio [84, 85].

The obesity hypoventilation syndrome can be successfully treated with continuous positive airway pressure (CPAP) or with bilevel non-invasive ventilation. Two Australian studies compared CPAP to bilevel NIV and found no significant difference between the two modes of treatment in outcomes of quality of life, ventilatory failure

and adherence [86, 87]. In the study by Howard et al., a multicentre double-blind trial compared the effects of initial treatment with nocturnal continuous positive airway pressure (CPAP) treatment to those of bi-level positive airway pressure (BiPAP) in 57 patients with obesity hypoventilation. The primary outcome measures included treatment failure, defined as hospital admission, persistent respiratory failure or non-adherence. Other secondary outcome measures included the effect on sleepiness and health-related quality of life (HRQoL). There was no significant difference between the two groups in treatment failure, nor in the secondary outcomes. The authors performed exploratory analyses and found that the only predictor of persistent respiratory failure, was baseline severity of respiratory failure [88]. The other Australian study by Piper et al. also compared the effects of CPAP therapy to those of bilevel ventilatory support (BVS) in 366 patients with obesity hypoventilation syndrome. The authors excluded patients with persistent severe hypoxaemia or CO<sub>2</sub> retention despite optimal CPAP therapy. The patients were randomly assigned to either therapy and were followed up for three months. The primary outcome was change in daytime CO<sub>2</sub> level, while secondary outcomes included quality of life, subjective daytime sleepiness, compliance with therapy and psychomotor vigilance testing. The results showed no significant difference between the two treatment arms in the primary outcome of daytime CO<sub>2</sub> levels. There was also no difference between the two groups in adherence to therapy, subjective daytime sleepiness or health-related quality of life questionnaire. On the other hand, there was a significant improvement in subjective sleep quality and in some aspects of the psychomotor vigilance test [86].

In another study by Masa et al., the authors compared lifestyle measures to non-invasive ventilation in patients with obesity hypoventilation syndrome without significant obstructive sleep apnoea. Outcome measures included daytime carbon dioxide levels as

well as assessment of sleepiness, health-related quality of life questionnaire and polysomnographic parameters. Volume targeted pressure support was the mode of ventilation and was adjusted according to a specified protocol. Non-invasive ventilation led to larger improvement in arterial carbon dioxide levels. The other parameters including sleepiness, polysomnographic parameters and health-related quality of life questionnaire also significantly improved.

For the purpose of this thesis, we shall be dealing with non-obesity related extrathoracic lung restriction.

## **1.8 Pathophysiology of lung restriction and hypoventilation due to extrathoracic causes**

Neuromuscular weakness and chest wall diseases are the two main groups of conditions causing extrathoracic lung restriction that will be dealt with in this research. In these two groups of conditions, both the reduction in compliance and muscle weakness respectively impair ventilatory function by restricting the ability to create enough negative pressure or vacuum during inspiration and to a lesser extent also restricting the capacity to induce the positive pressure required for forced expiration. The tidal volume is reduced ( $V_T$ ) and although the alveolar dead space ( $V_D$ ) is not increased, the  $V_D/V_T$  ratio is ultimately changed in favour of more dead space not available for ventilation[3, 42].

The pathophysiology underlying lung restriction is different between the two groups although some overlap exists. In simple terms, the respiratory muscles which may include the diaphragm are weak in neuromuscular disease; while in chest wall disease, the respiratory muscles are disadvantaged by the skeletal abnormalities causing them to work inefficiently [89]. As a result, there is failure of the respiratory system to deal

with the increased load on the already disadvantaged respiratory muscles that do not have the capacity to match the required work of breathing, a term that was described by Hillman et al. as “load-capacity imbalance” [89]. The difference in the pathophysiology of the lung restriction and hypoventilation between the groups is detailed below.

### **1.8.1 Pathophysiology of lung restriction and hypoventilation due to chest wall disease**

In chest wall disease; most commonly due to kyphoscoliosis; lung restriction can be quite severe with total lung capacity and vital capacity falling as low as 30% of their predicted values [10, 90]. The degree of restriction is directly affected by the angle of scoliosis as demonstrated in a cross-sectional study of 66 adolescents with non-surgically corrected idiopathic thoracic scoliosis[91]. In another study by Sawicka et al. [92], patients with non-paralytic kyphoscoliosis and paralytic kyphoscoliosis were compared to normal subjects in outcomes of ventilation and respiratory events overnight, by undergoing sleep studies. The results suggested that the degree of hypoventilation, as measured by the levels of hypoxaemia, rise in end-tidal transcutaneous CO<sub>2</sub> and respiratory events (mainly hypopnoeas), was directly related to the degree of lung restriction in these patients, when compared to normal subjects. The development of hypoventilation was directly related to reduced chest wall movement measured by placing magnetometers on the chest anteroposteriorly.

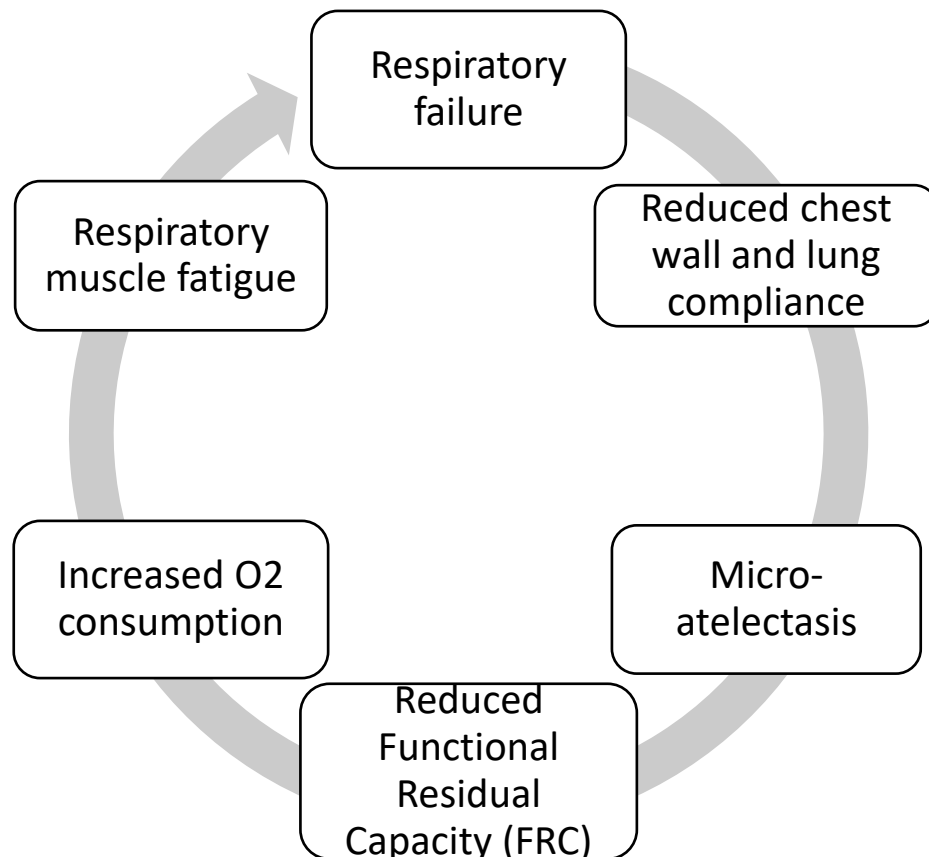
Anatomical malalignment of the thoracic spine and thoracic cage causes stiffness of the chest wall and affects the resting position of the respiratory apparatus leading to reduced functional residual capacity and total lung capacity. This leads to micro-atelectasis; which is not always seen on radiological studies; and ventilation-perfusion mismatch. Lung restriction develops due to reduced chest wall and to a lesser degree lung

compliance[10]. The reduction in lung compliance is due to micro-atelectasis from the relatively immobile chest wall. The respiratory muscles including the diaphragm become weaker and stiffer due to underutilisation. The diaphragm function is affected due to the mechanical disadvantage altering its position [93]. In a study by Cooper et al. [94], young adolescents with mild to moderate idiopathic kyphoscoliosis were studied before and after corrective spine surgery with Harrington rods and their lung function was compared with that of a group of healthy adolescents. Lung function was assessed using plethysmography and lung mechanics were assessed by inserting an oesophageal balloon. The index group had a measured mean total lung capacity  $75 \pm 13\%$  of predicted values. Static and dynamic lung compliance were reduced and so were the maximal inspiratory airway pressures and the peak expiratory flows. The subjects were then given positive pressure breathing at 25cm H<sub>2</sub>O for five minutes. Pulmonary pressure volume curves and dynamic compliance were compared before and after the manoeuvre using the oesophageal balloon technique. There was a significant improvement in dynamic compliance in the patients with low TLC with a mean value of 34%, as compared to subjects with normal TLC whose dynamic compliance improved only by 14%. When the patients were studied after the corrective spine surgery, there was a significant increase in maximum inspiratory airway pressures and peak expiratory flows. The authors concluded that the reduction in lung capacity in these patients with mild to moderate kyphoscoliosis was related partly to defective mechanical coupling between the inspiratory muscles and the thoracic cage [94].

In addition, in patients with chest wall disease, the ability to breathe efficiently requires greater respiratory effort for relatively small tidal breaths, which increases the work and oxygen cost of breathing. The increased oxygen consumption can reach three to five

times that of healthy individuals and contributes to respiratory muscle fatigue which in turn leads to respiratory failure, figure 1.3 [95].

During sleep, the inefficiency of the respiratory system in patients with chest wall disease becomes more obvious and symptoms of ventilatory failure or sleep disordered breathing, present earlier than daytime symptoms. The loss of stimulatory drive to breathe; that is present during wakefulness; causes inhibition of the neural stimulation of the respiratory muscles including the chest wall muscles and upper airway [11]. The former contributes to the development of hypoventilation and the latter predisposes the upper airway to collapse during sleep. As these muscles are already disadvantaged in chest wall disease by the mechanical properties of the chest wall, and given the drop in vital capacity in the supine position, respiratory failure can develop easily during sleep when total lung capacity and functional residual capacity reach a critical point.



**Figure 1.2 Pathophysiology of respiratory failure in chest wall disease**

## **1.8.2 Pathophysiology of lung restriction and hypoventilation due to neuromuscular disease**

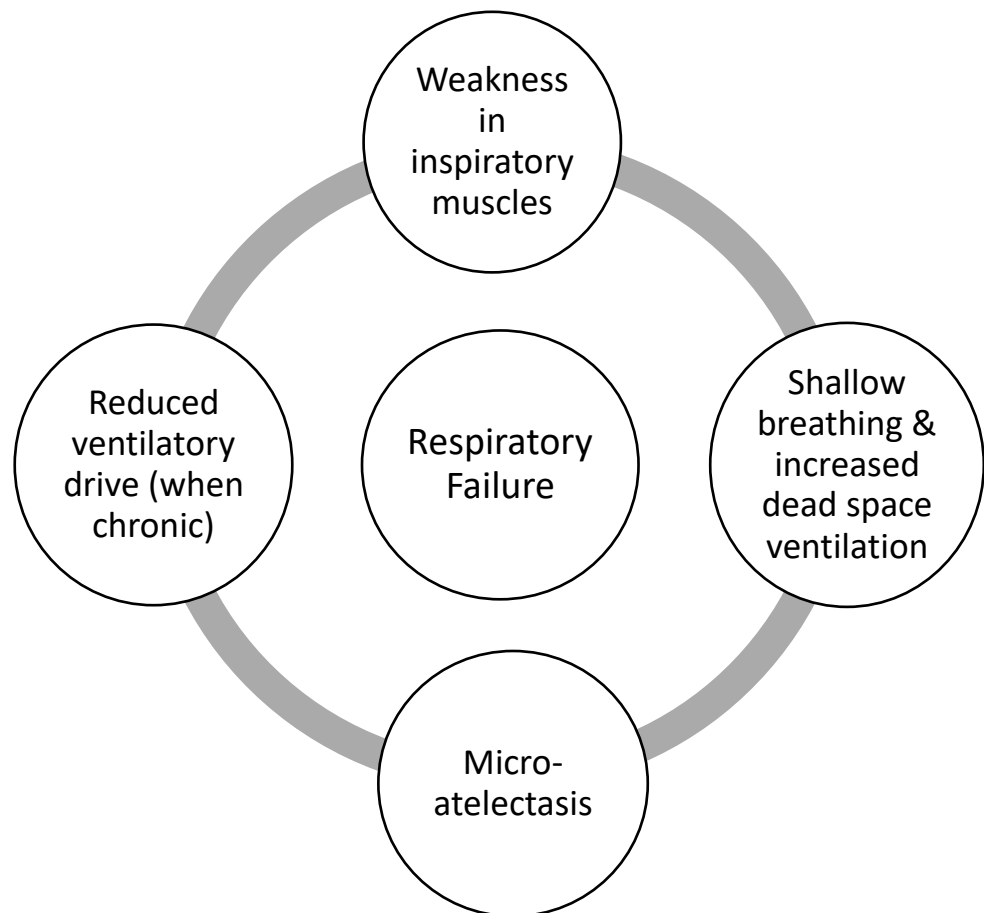
In neuro-muscular disease, lung restriction develops because of weakness in the respiratory muscles causing ineffective ventilation. The weakness can affect the intercostal muscles, the diaphragm and the upper airway muscles depending on the type of neuromuscular disease.

Because of muscle weakness, the vital capacity, total lung capacity, and function residual capacity are reduced. Change in postural FVC from sitting to supine position may be useful as a tool for predicting deterioration in muscle respiratory function although by itself it does not predict the need for ventilation unless accompanied by symptoms [37, 96]

Patients with neuromuscular disease breathe at smaller tidal volumes due to progressive inspiratory muscle weakness leading to basal atelectasis, which reduces the alveolar volume available for ventilation. This results in increasing dead space ventilation which in turn contributes to less gas exchange and ventilation-perfusion mismatch [97]. Physiologically, chest wall compliance may be reduced due to stiffness and lung compliance may be reduced particularly with longstanding disease due to reduced lung volumes. This may result from basal atelectasis, alteration in the elastic properties of the lung interstitium or increased surface tension (figure 1.3).

Weakness of the expiratory muscles, on the other hand, causes impairment of the cough mechanism leading to difficulty in clearing secretions, aspiration and lower respiratory tract infections. Weakness of the upper airway muscles leads to swallowing impairment which also contributes to the risk of aspiration. It can also cause sleep disordered breathing as will be discussed in detail later.

The combination of all of the above including microatelectasis, chest wall stiffness, sleep disordered breathing and the propensity to lower respiratory tract infections, eventually leads to type II respiratory failure [98, 99]. It is important to understand that depending on which muscle group is affected in neuromuscular disease, different symptoms may develop either individually or in combination. For example, weakness of the upper airway muscles may lead to obstructive sleep apnoea alone, whilst involvement of the intercostal muscles and diaphragm will lead to hypoventilation particularly during REM sleep [33]. Some patients will have a combination of upper airway obstruction and hypoventilation.



**Figure 1.3 Pathophysiology of respiratory failure in neuromuscular disease**

In most cases of neuromuscular weakness, there is normal or increased ventilatory drive, which fails to produce an adequate mechanical ventilatory response due to the underlying disease. The relatively normal ventilatory drive is due to intact feedback mechanisms to hypoxaemia and hypercapnia (figure 1.3); however, with time patients with chronic hypoventilation can develop a blunted response to hypercapnia [100]; which can reverse after initiation of mechanical ventilation and resetting of the central chemo-receptors[101].

In some cases, the ventilatory drive is reduced due to dysfunction in the chemoreceptors[102] or to neuronal dysfunction such as in patients with myotonic dystrophy and some patients with poliomyelitis [33]. The presentation of respiratory failure can be abrupt despite a gradual decline in lung function, often occurring in the setting of a respiratory tract infection or other illness. It is important to monitor these patients closely clinically as well as with serial lung function tests [103].

During sleep, further impairment of the respiratory apparatus develops due to the normal inhibition of wakefulness drive to breathe in addition to the muscle weakness. In normal individuals, muscle activity is altered during sleep as illustrated in the study of normal adolescents by Tabachnik et al. [104]. In this study, activity of the intercostal muscles was increased by 34% during NREM sleep, and diaphragm activity increased by 11% compared with wakefulness. On the other hand, during REM sleep, there was reduced intercostal muscle activity and ribcage contribution to measured vital capacity, while diaphragm activity was demonstrated to increase by 34%. In patients with neuromuscular disease loss of function of the diaphragm can cause significant REM hypoventilation.

## **1.9 Symptoms associated with restrictive lung disease**

In addition to the symptoms associated with their primary disease such as muscle weakness, difficulty with speech or swallowing, patients with extrathoracic restrictive lung disease often have respiratory symptoms as well as symptoms of sleep disordered breathing. Both problems are usually slowly progressive with the gradual worsening of their restrictive lung function. In general, the decline in lung function in patients with restrictive lung disease is slower than in those with neuromuscular disease due to the progressive muscle weakness that occurs in the latter group. In contrast to those with neuromuscular disease, patients with chest wall disease do not suffer from weakness in other muscle groups. For example, the degree of diaphragm muscle weakness when compared to neuromuscular disease is much less. In the latter, diaphragm weakness is neurally mediated and can be profound. On the other hand in chest wall disease due to musculoskeletal deformity, some diaphragm muscle weakness can develop with time due to the mechanical disadvantage and malpositioning of the diaphragm muscle [78]. The degree of diaphragm weakness, in this case, is not as profound and orthopnoea symptoms do not develop as early or as severely as those with neuromuscular disease. Patients with chest wall disease also generally do not have bulbar dysfunction that can cause aspiration and recurrent respiratory tract infections in the neuromuscular group. There is generally no weight loss due to progressive muscle weakness and / or reduced oral intake due to dysphagia.

### **1.9.1 Respiratory manifestations**

#### **1.9.1.1 Neuromuscular disease**

In neuromuscular disease, the main respiratory symptoms are shortness of breath, orthopnoea, and decreased exercise tolerance. Because of limited exercise due to limb

muscle weakness the symptoms can go undetected for years until the patient develops a chest infection, which not only leads to severe shortness of breath but also respiratory failure. Hypercapnia develops usually when the respiratory muscle strength reaches 30% or less. [105] In the long term, progressive type 2 respiratory failure can also lead to right heart failure or “cor pulmonale”.

Chest infections are not uncommon particularly due to susceptibility to aspiration from weakness of the pharyngeal and upper airway muscles. Bulbar dysfunction can impair upper airway reflexes particularly the cough reflex. The problem can be confounded by weakness of the expiratory muscles leading to ineffective cough and failure to clear secretions [96]. Other symptoms include orthopnoea secondary to diaphragm muscle paralysis. This can be confirmed by diaphragm screening radiologically. A chest radiograph usually shows an elevated hemidiaphragm, but the commonest test performed is referred to as the “Sniff test” which involves performing a sniff with ultrasound or fluoroscopy monitoring of the diaphragm. The healthy diaphragm moves downwards, while the denervated one moves upwards. [106]

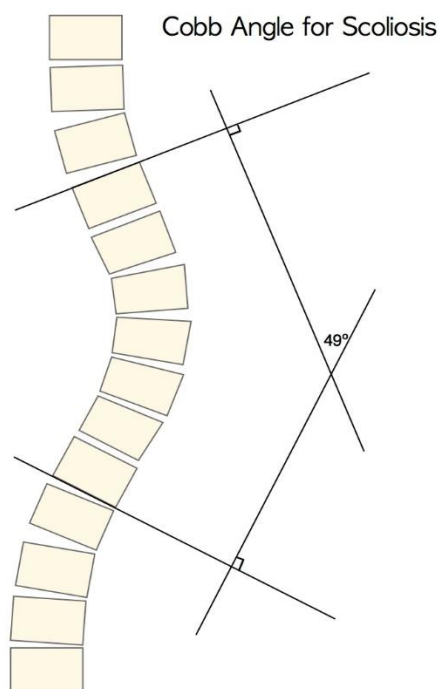
Lung function tests classically show a restrictive pattern with reduction in MIPs, MEPS and SNIP measurement, the latter being the most sensitive for assessment of diaphragm weakness.

### **1.9.1.2 Chest wall disease**

Patients with chest wall disease vary in their symptoms depending on their anatomy. This is best described in patients with kyphoscoliosis who can be classified as mild, moderate or severe degrees of thoracic deformity. The severity of the spinal deformity is assessed by measuring the Cobb angle on a radiograph of the spine. This is defined as the angle between two lines intersecting a parallel line running at the top and bottom

vertebrae of the scoliotic or kyphotic curves (figure 1.4). The greater the Cobb angle, the more severe is the deformity. Generally, patients with mild kyphoscoliosis (Cobb angle  $< 25^\circ$ ) have normal exercise capacity. Those with moderate kyphoscoliosis (angles  $25^\circ$  to  $70^\circ$ ) have reduced exercise tolerance and those with severe kyphoscoliosis (angle  $\geq 100^\circ$ ) have severe respiratory compromise and often respiratory failure[10].

Due to the rapid shallow breathing that is characteristic of patients with chest wall disease micro-atelectasis can develop and contributes to both the degree of lung restriction as well as to reduced lung compliance [107]. The dyspnoea is often multifactorial and may relate to cardiovascular factors and deconditioning as well as respiratory factors[10].



**Figure 1.4: Cobb angle for scoliosis**

## **1.9.2 Sleep disordered breathing**

Sleep disorders are quite common in patients with extrathoracic restrictive lung disease, in particular in those with neuromuscular disease. In a clinic population of 60 patients with a variety of neuromuscular diseases studied with ambulatory sleep studies, sleep disordered breathing was found in 42% of the clinic population [108]. The spectrum includes obstructive sleep apnoea, central and or mixed apnoeas, as well as nocturnal hypoventilation [109, 110].

Sleep apnoea can present with snoring, witnessed apnoeas, fragmented sleep, and excessive daytime sleepiness. Nocturnal hypoventilation presents with hypercapnia and hypoxaemia during sleep and can contribute to daytime hypoventilation. This hypoventilation can present with morning headaches and a feeling of cloudiness in the head due to vasodilatation from carbon dioxide retention.

Assessment of sleep disordered breathing in this cohort of patients often requires overnight full polysomnography with additional special monitoring [111]. A standard sleep study includes assessment of sleep structure through electroencephalography (EEG), cardiac rhythm through electrocardiography (ECG), eye movements through electrooculography (EOG), airflow through nasal pressure (Pnas), respiratory effort by assessing chest and abdominal movement through respiratory inductive plethysmography (RIP), limb movements through electromyography (EMG), muscle tone through submental electromyography (EMGc), arterial oxygen saturation through pulse oximetry (SpO<sub>2</sub>), sleep position through a position sensor or direct visualisation through video recording, as well as sound recording through a microphone or a calibrated sound level meter. Finally, an indication of light on or off is recorded.

Special monitoring in patients with suspected hypoventilation includes in addition to the above, carbon dioxide (CO<sub>2</sub>) monitoring usually through transcutaneous

measurement. The level of arterial carbon dioxide is often verified with direct arterial blood gas measurement in the evening and in the morning following the sleep study. Diaphragm contractility is an additional special measurement of effort, assessed using diaphragm electromyography (EMGd). Other types of effort assessment include scalene muscle electromyography (EMGsc). The gold standard for assessment of respiratory effort is via the insertion of an oesophageal balloon. This will be discussed separately below.

Patients who have sleep disordered breathing, often suffer from excessive daytime sleepiness due to the poor quality of their sleep. This can be assessed subjectively using a validated questionnaire such as the Epworth Sleepiness Scale. [112] The test is designed to detect excessive daytime sleepiness by questioning the subject about their chance of falling asleep or dozing (rather than just feeling tired) in a number of passive situations (Appendix 1). The scale has a maximum score of 24, with a score of 10 or more being considered pathological sleepiness.

Sleep disorders associated with the two categories of extrathoracic lung disease relevant to this research will be discussed separately below.

### **1.9.2.1 Neuromuscular disease**

Sleep disordered breathing is a common symptom in neuromuscular disease and the literature is rich in establishing the correlation and pathophysiology [33, 42, 113, 114]. In one small study, the incidence of sleep disordered breathing was 42% in patients with various neuromuscular disorders [108].

A number of factors contribute to the development of obstructive sleep apnoea in patients with neuromuscular disease. Pharyngeal muscle weakness due to myopathy or neuropathy from underlying disease causes the upper airway to collapse easily resulting

in obstruction. Macroglossia; particularly in patients with Duchenne muscular dystrophy; is another risk factor for obstructive apnoeic events in these patients due to reduced anatomical space in the upper airway. It is also thought that reduced lung volumes can contribute to the development of obstructive events due to reduced traction and stability of the upper airway [33, 115-119]. The events are more likely to occur during rapid eye movement sleep due to maximum inhibition of the upper airway and neck muscles[42]. Central events are reasonably common in neuromuscular disease[120]; although caution needs to be taken when analysing these events due to the presence of what has been labelled as “pseudo-central apnoea” as described by Smith et al. [121]. The latter events are obstructive events that masquerade as central events due to profound muscle weakness of the chest muscles and the diaphragm. The lack of movement of these muscles against a closed upper airway causes them to be misinterpreted as central events when in fact they are obstructive in nature as demonstrated in a study in patients with Duchenne muscular dystrophy [109]. Conversely, the opposite is also possible with paradoxical movement of the chest and abdomen in neuromuscular disease, being misinterpreted as obstructive events even when the upper airway is open [114].

Nocturnal hypoventilation is also common in patients with neuromuscular disease and for similar reasons tends to develop first during REM sleep due to muscle atonia in this phase of sleep [122]. A number of contributing factors lead to the development of nocturnal hypoventilation. These include supine position during sleep which in the setting of weak respiratory muscles; particularly the diaphragm; reduces lung expansion further. In the supine position, there is also increased upper airway resistance due to the easy collapsibility of the pharyngeal muscles leading to obstructive sleep apnoea. Another important factor is the physiological reduction in central drive that occurs

during sleep. Whilst this happens in normal individuals and causes a modest rise in CO<sub>2</sub>; particularly during REM sleep; the effect can be profound in the presence of severe muscle weakness and becomes clinically relevant. Eventually, daytime hypoventilation also develops and resets the central and peripheral chemoreceptors to higher levels of arterial CO<sub>2</sub>. The net effect is a cycle that perpetuates type II respiratory failure characterised by hypercapnia and hypoxaemia[42]. This can be complicated by “cor-pulmonale” as the disease progresses.

In addition to the above-mentioned physiological changes, the sleep disordered breathing as well as the associated hypercapnia and resultant fragmented sleep can lead to a degree of neurocognitive impairment. There is growing evidence that sleep disordered breathing is linked to an increased risk of cognitive impairment as summarised in a recent systematic review by Leng et al. [123]. The neuro-cognitive dysfunction can also be contributed to by the underlying disease, such as in patients with myotonic dystrophy patients who have a degree of cognitive impairment relating to the underlying disease itself.

### **1.9.2.2 Chest wall disease**

Chest wall disease is also associated with sleep disordered breathing, although to a lesser extent than in neuromuscular disease. Indeed, the two are commonly combined in studies in the literature [124, 125]. Very few studies have evaluated the incidence and spectrum of sleep disordered breathing in patients with chest wall disease alone, although a small study by Mezon et al., who evaluated five patients with kyphoscoliosis, found some form of sleep disordered breathing in four out of the five patients who exhibited a range of abnormalities from mild to severe [126].

Chest wall disease causes nocturnal hypoventilation by a number of mechanisms as described in the relevant section above. Other forms of sleep disordered breathing may co-exist; such as obstructive sleep apnoea; if the patients have the typical anatomical features that predispose them to upper airway collapse during sleep. This would include morbid obesity, retrognathia, nasal passage obstruction or small mouth and crowded upper airway. This not particularly different to normal population, although upper obstruction can occur in the absence of these classical features in patients with severe cervical kyphosis causing fixed head and neck position. In addition, reduced lung volumes in this group of patients, particularly the expiratory reserve volume, may make them more susceptible to upper airway collapse as described above [115-119].

### **1.9.3 Neuro-cognitive impairment**

Neuropsychological cognitive impairment is common with sleep disordered breathing and can result from sleep fragmentation and apnoea related hypoxaemia during sleep [127]. Underlying mechanisms of neurocognitive impairment in sleep disordered breathing are emerging and include hypoperfusion, endothelial dysfunction and neuro-inflammation secondary to intermittent hypoxaemia [128]. Neurocognitive impairment can occur with neuromuscular disease; however, it is an area that has been poorly studied and understood. In this systematic review by Orsini et al., patients with neuromuscular disease displayed variability and heterogeneity in the degree of neurocognitive dysfunction which included a broad range of functions such as memory tasks, naming and visuo-spatial abilities [129].

On the other hand, there is very limited literature available regarding neurocognitive assessment in chest wall disease. Whilst this has been recognised as a possible

symptom, the link relates more to the presence of sleep disordered breathing in this cohort of patients than a direct relationship.

During acute or acute on chronic type II respiratory failure, hypercapnia can cause disorientation, confusion, drowsiness and can lead to coma if not identified and treated promptly.

A number of tasks have been developed to perform neuropsychological testing. A well-validated test is the Psychomotor Vigilance Task (PVT). The test measures a visual reaction time when a light appears at random intervals on a hand-held device. It has been used and validated to test the effect of sleep deprivation on daytime performance and correlated well to the hours of sleep in the days prior [130-134].

## **1.10 Measurement of oesophageal pressure as a surrogate for intra-pleural pressure**

Measurement of pleural pressure is useful in studying lung mechanics and work of breathing. It is also useful to assess muscle activity of the inspiratory muscles, as during inspiration the pleural pressure decreases to allow the lungs to expand [10]. Negative deflections in pleural pressure can be used to detect respiratory effort associated with inspiration. Measuring oesophageal pressure (Poes) is a less invasive method of assessing pleural pressure (Ppl) than direct measurement by inserting a catheter into the pleural space. A more accurate description is that the changes in oesophageal pressure reflect changes in the pleural pressure. This is useful in a number of ways. It can be used to assess respiratory effort either during spontaneous breathing or supported ventilation with or without the use of a gastric balloon to assess transdiaphragmatic pressure[135]. It can also be used to assess the “work of breathing”; defined as the cost

of energy to overcome the elastic, resistive and inertial forces generated by the lungs, chest wall and respiratory apparatus to accomplish the act of breathing[10].

This method of measuring the oesophageal pressure has been described for more than 100 years and validated by a number of studies. The technique was discovered by Ceradini who did not publish his work; however, his name was mentioned by Luciani, the first to report this method. Later on, it was described by Mead et al. that the technique became more popular when Buytendijk published his work in this area[136]. There have been few reported studies of directly compared measurements of pleural pressure (Ppl) and oesophageal pressure. In the study by Mead et al., direct comparison was made in seven subjects by inserting an air-filled oesophageal balloon to measure oesophageal pressure and a catheter inserted in the pleural space directly by creating a small pneumothorax to measure pleural pressure. There was good correlation between the two pressures with less variation in the upright than in supine position[137]. The increased variation in the supine position is thought to be secondary to the weight of the mediastinal contents on the oesophagus [138]

A number of methods of measuring oesophageal pressure have been described in detail. Various assemblies have been in use including a fluid-filled system, or an air-filled balloon catheter system. The latter is more commonly used and was chosen for this project. The catheter itself is made from stiff polyethylene tubing and needs to be fenestrated spirally in the part covered by the balloon. The balloon itself is made from rubber and is tied neatly over the end of the catheter. Short balloons (2-3 cm), as well as long balloons (10-16 cm), have been used. Intermediate length balloons are most commonly used. The balloon is best positioned in the mid oesophagus to avoid artefacts from transmitted pressures. In the upper oesophagus pressure variations; not due to changes in pleural pressure; can be seen due to tracheal compression of the oesophagus.

In the lower part of the oesophagus pressure variations can be too high from point to point with a greater effect of body posture on measurements [136, 139, 140].

Measuring the frequency response of the system is standard practice to avoid an over or underdamped recording. This can be achieved up to a frequency of 32 Hz [141]. Resistance and compliance of the system should be checked for similar reasons. If the catheter is too compliant, this will lead to a dampened signal. If there is a narrowing in the tubing (i.e. increased resistance) the transmission of signal could be affected. Commercially available catheters can be purchased directly for the purpose of measuring oesophageal pressure and do not need the latter steps as resistance and compliance are already tested by the manufacturing company.

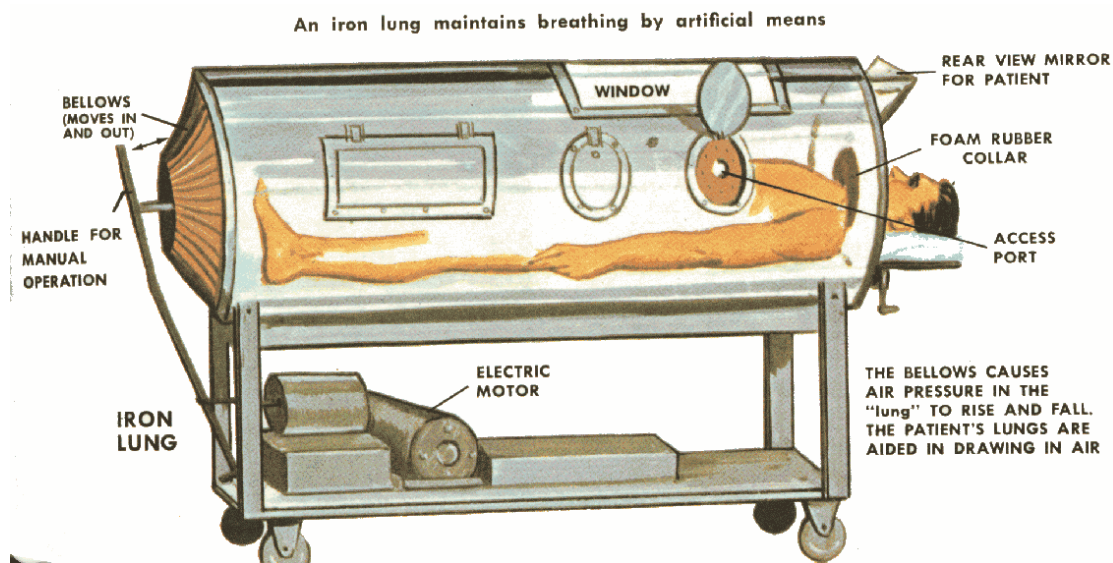
## **1.11 Treatment of respiratory failure in extrathoracic restrictive lung disease**

### **1.11.1 History of non-invasive ventilation**

The concept of ventilation was introduced by Andreas Vesalius, a Belgian professor of anatomy in the 16<sup>th</sup> century who contributed immensely to the current understanding of the respiratory system and introduced the idea of possible artificial ventilation. Robert Hook, who was a philosopher and a scientist, performed the experiment in the 17<sup>th</sup> century to ventilate the chest of a dog by using bellows to generate flow of gas into the airway then into the lungs.

Negative pressure ventilation was the first mode of therapy, developed in the early 19<sup>th</sup> century in different forms, and used to support people with chronic ventilatory failure from extrathoracic causes. The idea was to use sub-atmospheric pressure in an enclosed chamber to support the respiratory muscles in their movement and to thereby provide adequate ventilation. One such early “body enclosing boxes” was invented by Alfred

Jones in 1864. This used a plunger to either decrease the pressure in the box to initiate inspiration or increase the pressure in the box to cause expiration. The “Iron Lung”, a common device used during the polio epidemic in the early 1900s, was invented in 1876 by Alfred Woillez who called it the “Spirophore” with the concept modified later by other inventors such as Drinker and Shaw in 1929. The concept involves having the patient in an enclosed tube usually made from iron with the head protruding from one end, and bellows moving in and out on the other end to generate both negative and positive pressure in order to aid the ailing respiratory muscles (figure 1.5). Thousands of patients were ventilated by this means during the polio epidemic in the 1950s (figure 1.6). Many other devices such as the “pneumatic chamber”, the “respirator room” and the “ventilation room” were also developed[142]. Other inventions such as the “Cuirass” ventilator involved wearing an inflexible shell over the chest and abdomen. The main advantage of this device over the iron lung is that it is easily portable making care of the patient much easier. Modern cuirass ventilators are still used around the world in some respiratory intensive care units[143, 144].



**Figure 1.5: Illustration of “iron lung” concept**



**Figure 1.6: “Iron lung” ward during the polio epidemic**

All these devices described above were based on the concept that the negative pressure generated inside these devices and rooms expanded the chest, abdomen and hence the lungs. Since the advent of positive pressure ventilation, the management of type II respiratory failure and hypoventilation has evolved significantly and the use of these negative pressure ventilators has gradually declined.

New therapies have emerged in the last twenty years including diaphragm pacing which can be used in a subset of patients. Diaphragm pacing has been used to wean ventilator dependent patients off mechanical ventilation and can work as an alternative therapy. It has the advantages of greater comfort, easier mobility for the patient and avoidance of possible ventilator-associated complications. Patients with two types of conditions may be considered for diaphragm pacing: spinal cord injury and central hypoventilation syndrome. The concept is that these patients should have intact phrenic nerve, diaphragm muscle and lung parenchyma. One of two approaches is generally taken. The first is referred to as “intrathoracic diaphragm pacing”; where radio-frequency stimulation of the phrenic nerve is used through video-assisted thoracic surgery. The second is referred to as “intraperitoneal diaphragm pacing” where electrodes are placed directly over the diaphragm through a laparoscopic procedure. Patient selection is very important before this procedure can be considered in order to ensure the appropriateness of treatment for the individual candidate[145]. In one series over a ten-year period, twenty ventilator dependent patients underwent diaphragm pacing using the radio-frequency method. There was a high success rate in weaning off mechanical ventilation with 18 patients out of 20 being successfully weaned with no significant complications [146].

### **1.11.2 Non-invasive positive pressure ventilation**

Positive pressure ventilation can be achieved by either invasive ventilation via endotracheal tube or tracheostomy or by non-invasive ventilation. Long term ventilation via endotracheal tube is not possible or feasible due to the significant complications that can develop, including a range of barotrauma effects as well as ulceration and later on narrowing or perforation of the trachea. Ventilation via tracheostomy has long term side effects and requires permanent supportive care usually by trained staff. This includes the need for frequent suctioning, toileting and pressure care. Tracheostomies have to be changed every few months by experienced staff as they tend to block from retained inspissated secretions. Regular changing of the tracheostomy tubes also prevents the formation of granulation tissue; a commonly encountered complication [147].

The most attractive and practical option for providing long term ventilatory support is non-invasive positive pressure ventilation. This has been a major development in the treatment of respiratory failure, including extrathoracic restrictive lung disease. Although it was first studied in the 1930s[148], it only became widely available and an established form of therapy in the early 1980s and flourishing in the 1990s, since when it has gradually replaced negative pressure ventilation [149-151].

Researchers from Sydney, Australia led by Colin Sullivan reported successful treatment of five patients with severe obstructive sleep apnoea with continuous positive airway pressure (CPAP). Using two soft plastic tubes connected to a wide bore tube and sealed in the patients' nares with medical grade-silicone rubber, this arrangement was strapped onto the patients' face and connected to a vacuum-cleaner blower motor. The apparatus reversed occlusion of the upper airway and improved oxy-haemoglobin saturation [152]. The term CPAP in NIV terminology refers to one level of positive pressure

ventilation applied throughout the respiratory cycle including inspiration and expiration. Another form of NIV referred to as bilevel positive airway pressure ventilation (BiPAP) indicates having two levels of positive pressure, a higher pressure during inspiration referred to as “inspiratory positive airway pressure” (IPAP) and a lower pressure during expiration referred to as “expiratory positive airway pressure” (EPAP). The difference between IPAP and EPAP is referred to as “pressure support” (PS) [153, 154]. Whilst there are some similarities between CPAP and NIV in their concept of being a form of non-invasive positive pressure ventilation, their use in clinical practice is different. CPAP is currently used in the acute setting for treatment of pulmonary oedema. It is also used long term for treatment of obstructive sleep apnoea due to upper airway obstruction. BiPAP is mainly used for treatment of respiratory failure. The EPAP component aims to overcome upper airway obstruction and IPAP to overcome hypoventilation. The worse the hypoventilation, the higher the pressure support required. For the purpose of this research, NIV refers to bilevel ventilation [153, 155].

Non-invasive ventilation can improve survival and reduce morbidity in respiratory failure secondary to restrictive lung disease from neuromuscular or chest wall disease; although long term large volume multicentre studies are still required in this area. A plethora of clinical studies and systematic reviews have shown consistent benefit in reversing the clinical symptoms of type II respiratory failure including respiratory and sleep-related symptoms. In particular, NIV has been well established in the management of ventilatory failure from neuromuscular disease and chest wall diseases [156-160]. In a subgroup of patients with motor neurone disease and Duchenne muscular dystrophy who have shorter life expectancy than other neuromuscular

conditions, there was a survival benefit; however, the evidence is limited and more research is required [47, 52, 56, 59, 68, 69, 156].

Clinically NIV leads to improved quality of life, sleep quality, nocturnal gas exchange, daytime hypercapnia and reduces hospital admissions. These improvements have been achieved in both patients with neuromuscular disease and those with chest wall disease [51, 61, 156, 158, 159, 161-167]. Drawing from the motor neuron disease literature, there may also be beneficial effects on preservation of ventilatory function by avoiding micro-atelectasis and repositioning of the respiratory muscles [168].

The delivery of non-invasive positive pressure ventilation for treatment of extrathoracic restrictive lung disease normally refers to ventilation with a mask interface or a mouthpiece. Different types of masks exist and can simply be divided into full face masks (covering the nose and the mouth), nasal masks (covering the entire nose and not covering the mouth) and nasal prongs (inserted into the nostrils but not covering the entire nose). The latter two can be problematic if the patient breathes through his/her mouth which can cause significant leak leading to problems with cycling and dys-synchrony. “Triggering” of the ventilator refers to the initiation of inspiration by triggering an inbuilt pressure or flow sensor by the patient, although the latter has become more popular. “Cycling” refers to the termination of inspiration and changing to expiration to allow the patient to breathe out. “Patient-ventilator dys-synchrony”, is defined as uncoupling of the patient’s respiratory effort and the onset of ventilator pressure support for at least ten seconds and three consecutive breaths[169], and can impair the effectiveness of ventilatory support.

The option of a non-invasive method of long-term ventilation has a number of benefits compared to invasive ventilation via a permanent tracheostomy. As the former is delivered via either a nasal or full-face mask, there is less trauma to the airway, as well

as fewer cutaneous infections around the tracheostomy and fewer respiratory infections. Care needs are less, obviating the need for regular suctioning and frequent changing of dressings in the presence of skin infections. Other benefits include the preservation of phonation.

A number of mechanisms have been postulated to explain the observed improvements in gas exchange in type II respiratory failure, following the institution of NIV. It is thought that Non-Invasive Ventilation does not significantly improve respiratory muscle strength or lung compliance; however, it has been suggested in some studies that NIV induces a resetting of the central chemoreceptors [157].

### **1.11.3 Modes of non-invasive ventilation**

There are two main modes via which non-invasive ventilation can be delivered. One relies on delivering a guaranteed volume of air and this is referred to as “volume cycled ventilation”. The volume is constant although the pressure required to deliver the volume is variable. The ventilator is set by dialling the desired tidal volume ( $V_t$ ), inspiratory flow and the breath rate as the basic settings. The second mode relies on delivering pre-set pressures to achieve a target volume “pressure cycled ventilation”. The pressure here is the constant and the delivered volume becomes the variable. The ventilator is set by dialling an inspiratory pressure (IPAP), an expiratory pressure (EPAP), with the difference in pressure termed pressure support (PS). The inspiratory time is set to a minimum and a maximum usually termed ( $T_{iMin}$ ) and ( $T_{iMax}$ ) respectively. The ventilator can be set with either no breath rate in “spontaneous mode” or with a set breath rate in “timed mode” and “spontaneous timed mode” [170, 171].

As the above settings can become a problem in some patients either because of under-delivery of the desired volume of ventilation in pressure-cycled mode or because of

over-pressurisation of the airway in volume cycled mode, various more sophisticated modes have been developed that can combine the two modes. The modes of delivery rely on the same principles of delivering either pressure or volume; however, the newer modes attempt to deliver a guaranteed volume or pressure to ensure adequate ventilation. Examples of this are “volume-assured pressure support ventilation” (VAPSV) and “pressure regulated volume control” (PRVC). Other modes of ventilation exist but are beyond the scope and the purpose of this research.

Pressure cycled ventilation is generally conceived of as a more comfortable method of ventilation than volume-cycled, although limited trials have compared the two modes and found no significant difference [172]. Pressure-cycled ventilation also has the significant advantage of leak compensation as the ventilator is trying to achieve the preset pressure. Both of these features make it more attractive to use than volume cycled modes. In fact, in a large European survey conducted in 2001-2002 and published in 2005 [173] that involved 22,000 patients in 483 centres in 16 countries. The patients were divided into three categories: either having lung parenchymal pathology, chest wall disease or neuromuscular disease. The authors calculated that volume cycled ventilation was used in patients with parenchymal lung disease with a prevalence of 15%, in those with restrictive lung disease at 28% and in the remaining category of neuromuscular disease patients at 41%. The most common mode of home mechanical ventilation (HMV) was pressure cycled ventilation.

A similar pattern of preference for pressure-cycled HMV was observed in Australia and New Zealand, where 95.5% undergoing HMV were receiving pressure-cycled HMV in a large multicentre survey. In this study by Garner et al. [174], data on 2725 patients with chronic respiratory failure were collected across 28 centres to study the pattern of HMV across the two countries. The study included patients with different disease

aetiologies including chronic obstructive pulmonary disease (COPD), neuromuscular disease (NMD), obesity hypoventilation syndrome (OHS) and chest wall disease (CWD). The indication for prescription of home mechanical ventilation varied between Australia and New Zealand. Neuromuscular disease was the commonest indication for HMV in Australia whilst obesity hypoventilation was the most prevalent indication in New Zealand. When compared to Europe, the prevalence of home mechanical ventilation was higher in Australia and New Zealand at 9.8 versus 6.6 per 100,000 population; in the previously cited European study, although the European study was done 10 years earlier and the HMV rate is thought to be likely higher when adjusted for timeline. Overall the high prevalence of home mechanical ventilation prescription for patients with obesity hypoventilation syndrome; as the commonest indication; would have contributed to the fact that pressure-cycled ventilation was the commonest mode of ventilation, as volume cycled ventilation is almost certainly never used for this group of patients. In fact, in patients with obesity hypoventilation, continuous positive airway pressure (CPAP) is often adequate as demonstrated in two previously described Australian studies [86, 87]. Nevertheless; this alone does not explain the dominance of pressure-cycled ventilation in this large survey. Having said that, historically, in some patients who have severely restricted lungs a volume cycled ventilator may be preferred, possibly due to the very stiff lungs, making it difficult for a pressure-cycled ventilator to achieve the desired tidal volumes; however, this has not been validated by clinical studies.

The two modes of ventilation namely volume cycled and pressured cycled ventilation have been compared in a number of studies. Most studies were done in either heterogeneous groups of patients or with non-matched settings making results difficult to interpret; however, no major differences were found in ventilation parameters [175,

176]. A study by Tuggey et al., which was a single-blinded randomised study that directly compared volume cycled and pressure cycled ventilation in patients with chest wall disease in a cross over design including a washout period of two weeks. The participants were ventilated via a Breas PV403 ventilator which was capable of providing volume and pressure control ventilation. Twelve patients with chronic respiratory failure due to chest wall disease completed the study. They were all on pressure-controlled ventilation prior to commencing the study. The participants were assessed for sleep quality, daytime gas exchange parameters as measured by arterial blood gases, lung mechanics, ventilatory drive, health status or daytime functioning using full polysomnography and a pneumotachometer the night after each allocated mode. There were no significant differences in efficacy of ventilation or in sleep quality, health status or daytime function [172].

#### **1.11.4 Setting of non-invasive ventilation**

The settings used to provide non-invasive ventilation depend on the underlying pathophysiology of the condition causing type II respiratory failure as well as the respiratory mechanics of the condition. The settings will also vary according to patient-specific anatomy and preferences. The main four groups of patients with type two respiratory failure who need non-invasive ventilation are obesity hypoventilation syndrome (OHS), neuromuscular disease and chest wall disease and chronic obstructive pulmonary disease generally require different ventilator settings and will be discussed separately below, except for the latter as this is not relevant to this research.

There are no current evidence-based recommendations on how to set up non-invasive ventilation, which is usually done according to local experience. The initial settings are usually empirical and aim at improving gas exchange to an acceptable level. Other

secondary gains usually follow, including better sleep quality at night and improved daytime level of function [155]. During setup different masks are assessed for good seal to minimise leak and taking into account patient comfort. The settings are aimed at matching the patient's ventilatory needs and this differs from one patient to the other. Monitoring after initiation of ventilation is essential particularly if the patient was implemented as a day admission [177]. Care needs to be taken to avoid underventilation to ensure adequate night-time gas exchange and better sleep quality [135] or overventilation that can cause glottic closure, particularly in patients with motor who have a sensitive upper airway from bulbar involvement [178].

Newer technologies have emerged to facilitate remote monitoring of these patients where the data from the ventilator is uploaded online for easier access by the treating clinicians, and also to minimise travel needs for these relatively frail patients. Similarly, the use of telehealth for clinical consultation has become a standard of care in many ventilation centres, particularly for those who live in remote areas or those who have severe debilitating physical disabilities. Many centres do a follow-up polysomnography for fine titration of settings to correct any residual hypoventilation or to troubleshoot problems with synchrony between the patient and the ventilator, triggering related issues or leak, which has been suggested in the literature [114, 154, 179].

Recently, researchers have been trying to optimise the prescription of non-invasive ventilation in patients with chronic hypercapnic respiratory failure.

A recent Australian single centre blinded randomised control study assessed whether non-invasive ventilation as determined by polysomnographic titration was associated with less patient-ventilator asynchrony and arousals than sham titration, in patients with medical stable chronic hypercapnic respiratory failure. The study also assessed sleep quality, degree of somnolence, health-related quality of life as well as nocturnal gas

exchange parameters. A total of 60 participants were randomised successfully. The participants were patients naïve to NIV who were referred for long term non-invasive ventilation to the study centre. The study included all comers including patients with motor neurone disease, which formed the majority of participants, other neuromuscular disease, restrictive thoracic disorder, obesity hypoventilation syndrome and overlap syndrome (chronic obstructive pulmonary disease with obstructive sleep apnoea). The patients underwent daytime titration followed by an acclimatisation period before they returned back for either polysomnographic titration (PSG group) or sham titration (control group). The results showed that in the polysomnographic titration group there was less patient-ventilator asynchrony than in the control group. There was no significant difference in the number of arousals, nor in sleep quality, somnolence or health-related quality of life. Nocturnal gas exchange was similar between the two groups [180].

The study highlighted that implementing patients on the appropriate non-invasive ventilation settings was associated with less patient-ventilator asynchrony; however, this did not translate into better quality sleep or improvement in symptoms in general. The authors acknowledged that the study may have been underpowered.

As described above in the study by Georges et al., the authors assessed the impact of upper airway obstruction in patients with amyotrophic lateral sclerosis (ALS) on survival and concluded that the presence of such obstruction is associated with poorer prognosis [49]. More studies are still required to optimise ventilation settings in the different groups of patients with chronic type two respiratory failure.

#### **1.11.4.1 Obesity hypoventilation syndrome (OHS)**

Non-invasive ventilation may be used to treat selected patients with obesity hypoventilation syndrome in select patients.

The aims of providing assisted ventilation in this patient group are two-fold: first, to overcome the upper airway resistance particularly if there is co-existing obstructive sleep apnoea which is present in 90% of such patients [181]; and second, to overcome the reduction in chest wall compliance due compression of the rib cage and abdomen by the excess adipose tissue. This group of patients can often be adequately treated with continuous positive airway pressure (CPAP) alone which can correct hypercapnia in a manner similar to bilevel ventilation as demonstrated in two Australian studies. In the first study by Piper et al., 36 patients with OHS were randomised to either CPAP therapy or bilevel ventilatory support (BVS). The CPAP group had a mean BMI of  $52 \pm 7$  and a baseline median and interquartile range (IQR) PaCO<sub>2</sub> of 52 (49-55) and the BVS group had a mean BMI  $54 \pm 9$  and a baseline median (IQR) PaCO<sub>2</sub> 49 (47-57). There was no difference in the reduction in carbon dioxide (CO<sub>2</sub>) levels between the two groups after three months of treatment. There was no significant difference in sleep parameters after initial assessment; however, there was a subjective improvement in sleep quality in the bilevel ventilatory support group according to the Pittsburgh sleep quality index (PSQI) at three months. There was also an improvement in psychomotor vigilance testing in the slowest reaction times [86].

The second study by Howard, et al. was a multicentre trial, following up 57 newly diagnosed patients with obesity hypoventilation syndrome on either CPAP or bilevel ventilation for a period of three months. There was no significant difference between the two modes in treatment failure or correction of respiratory failure, although patients on bi-level ventilation tended to have a lower PaCO<sub>2</sub> particularly at one month

assessment from baseline. The most important predictor for persistent ventilatory failure was the initial PaCO<sub>2</sub> before commencement on therapy. The study also assessed the effect of each mode on sleepiness; as assessed by the Epworth sleepiness scale and also health-related quality of life questionnaire (HRQoL) as secondary outcomes. There was a similar improvement in both parameters with no significant difference between the two modes. [87].

Some patients with severe type two respiratory failure from OHS may require bilevel ventilation if they fail CPAP therapy. The typical settings usually involve a high expiratory airway pressure, manually titrated to overcome upper airway obstruction and a relatively small pressure support to correct for hypercapnia [153], although there are no current guidelines available on optimal pressures in this group of patients.

#### **1.11.4.2 Chest wall disease (CWD)**

Patients with extrathoracic lung restriction secondary to chest wall disease benefit from non-invasive ventilation to correct hypoventilation and alleviate their symptoms as previously described. There are no current guidelines on choosing the type of ventilator and the appropriate settings when patients are commencing ventilation[182]. The process of implementation of non-invasive ventilation can vary from one respiratory centre to another depending on local practices and expertise; however, there are some general concepts that are important to consider. Most patients with chest wall disease do not have respiratory muscle weakness except for patients with poliomyelitis who can have intercostal muscle and diaphragm muscle weakness. Over time with chronicity of the disease, non-polio patients can also suffer from loss of muscle function due to muscle deconditioning and the mechanical disadvantage from musculoskeletal abnormalities. Upper airway muscles are not generally affected by the disease process

in chest wall disease, and upper airway protective mechanisms are generally intact, although during sleep upper airway obstruction can be encountered in some patients.

Due to the mechanical properties of the thoracic cage, patients with lung restriction from chest wall disease have stiff chests with reduced chest wall and to a lesser extent lung compliance.

In the absence of clear recommendations on which ventilator settings to use for this group of patients, consensus guidelines are largely followed. These guidelines have been published by the NPPV Titration Task Force of the American Academy of Sleep Medicine [154] and the consensus conference on clinical indications [182]. They recommend that in general EPAP should be increased if there is evidence of upper airway obstruction as measured during polysomnography. IPAP and pressure support should be increased if there is evidence of hypoventilation (rise in PCO<sub>2</sub> more than 10mmHg from baseline, or if oxygen saturation (SpO<sub>2</sub>) remains below 90% for five minutes or more in the presence of low tidal volume). The use of a backup rate is generally recommended (such as inST mode) in patients with central hypoventilation, low respiratory rate or when there is failure to trigger the ventilator. In some patients with severely compromised lung function; who have significant difficulty triggering; the use of a volume cycled ventilator or volume-assured pressure cycled ventilator may be necessary.

#### **1.11.4.3 Neuromuscular disease**

Neuromuscular disease is a heterogeneous group of diseases and differences in pathophysiology and symptomatology between subtypes can dictate ventilator settings. As in the case of chest wall disease, there are not many studies on how to set up this

group patients on non-invasive ventilation and consensus guideline are generally followed.

The settings on NIV may be similar between the patients with neuromuscular disease and chest wall disease, due to the shared aspects of extrathoracic ventilatory defect. In fact, in the study by Piper and Sullivan, which assessed the effect of six months long term nasal ventilation on spontaneous breathing after withdrawal of ventilation, when the two groups were compared, apart from the maximal inspiratory pressure being lower in the neuromuscular group at baseline, there were no other difference in outcome, including parameters of gas exchange at follow up [183].

Despite some of these similarities between patients with neuromuscular disease and those with chest wall disease, there are other distinct differences that can affect the mode of ventilation and its delivery. Patients with neuromuscular disease can have respiratory muscle weakness due to the underlying disease. This may involve the intercostal muscle, the diaphragm or both. The patients may be unable to initiate enough inspiratory flow to trigger a pressure-cycled ventilator if it is set up in spontaneous or spontaneous timed mode. In this case, the use of spontaneous mode would not be suitable. The use of spontaneous timed mode or even changing to a timed (T) mode, which is not commonly used currently, may be necessary. Another option is to consider using either a volume-cycled ventilator that guarantees the delivery of certain preset volumes; or a volume-assured pressure cycled ventilator with guaranteed minute ventilation settings, as the name implies [154]. The latter has not been shown to be superior to conventional bilevel ventilation [184, 185].

Another symptom that may be encountered in neuromuscular disease, is upper airway muscle weakness. This can lead to upper airway obstruction causing obstructive sleep apnoea, which necessitates increasing expiratory positive airway pressure. If the patient

has co-existing hypoventilation, they may end up on high inspiratory positive airway pressures to deliver enough pressure support to correct the impaired gas exchange. In addition, upper airway muscle weakness can lead to bulbar dysfunction with difficulty swallowing, phonating, coughing, and clearing secretions. In this case, the use of a nasal mask is preferred to a full-face mask which can lead to retained secretions behind the mask. This can be particularly problematic if the patient has significant weakness in the upper limbs limiting the ability to release or manoeuvre the mask. In some cases, if bulbar dysfunction is quite severe, non-invasive ventilation may not be possible and the insertion of a tracheostomy may be necessary [186]. This has a different setup but is beyond the purpose of this thesis.

Patients with neuromuscular disease can also have generalised muscle weakness and often end up with very limited mobility being wheelchair-bound. In this instance, the patients may prefer mouthpiece ventilation. Although it is less commonly used than nasal or full-face mask ventilation, it does have the advantage of being more comfortable, and more ability to speak. It is also useful in patients who cannot tolerate other forms of non-invasive ventilation [187].

### **1.11.5 Modes of pressure-cycled ventilation**

Pressure cycled ventilation can be delivered in a spontaneous mode, where ventilator delivered breaths can only be triggered by the patient, or timed mode where the ventilator delivers a preset rate with no contribution from the patient or a spontaneous timed mode, which is a combination of the previous two modes, where the patient can trigger the ventilator but also receive a preset backup rate. In spontaneous mode, inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) values are set to achieve a target tidal volume according to the patient's

characteristics and needs; however, the patient controls the respiratory rate as they have to initiate the mechanically delivered breaths. The patient also controls the cycling of the ventilator to switch from inspiration to expiration. In other words, in true full spontaneous mode, there is no pre-set breath rate and no pre-set triggering or cycling time. According to the American Academy of Sleep Medicine guidelines, spontaneous mode should be the default setting for starting non-invasive ventilation unless there is ongoing hypoventilation while on spontaneous mode due to low intrinsic respiratory rate or central apnoeas [154].

Theoretically, spontaneous mode is the most comfortable and synchronous mode of ventilation as it is completely controlled by the patient. In reality, this may not be the case, as problems can occur due to failure of triggering the ventilator or unintentional premature or prolonged cycling into expiration.

The spontaneous timed mode, on the other hand, guarantees a pre-set number of breaths delivered in addition to patient-initiated breaths and is more likely to ensure adequate ventilation. It is generally recommended in patients with central hypoventilation or those who have a significantly reduced respiratory drive [154]. However, there is potential for patient-ventilator dys-synchrony, patient discomfort, triggering problems and over-ventilation on spontaneous timed mode [169, 188, 189]. Overventilation can also lead to intermittent glottic closure resulting in complete cessation of breathing due to development of hypocapnia from over ventilation [190, 191].

All these can arise as the ventilator is preset initiate breaths at regular intervals, while the patient may attempt to initiate inspiration or expiration at their own time.

Another mode of ventilation that is available on devices delivering non-invasive ventilation is the “timed mode”. This refers to ventilation with a fully timed back up rate which does not allow for any spontaneous breathing. This mode is rarely used as it

does not synchronise with the patient's breathing, making its use potentially more uncomfortable than spontaneous or spontaneous timed modes [151]. It is mainly recommended if there is severe underlying central hypoventilation or central apnoeas at baseline or during NIV titration that is not adequately controlled with spontaneous-timed mode [154].

### **1.11.6 Outcomes of non-invasive ventilation in restrictive lung disease**

Non-invasive positive pressure ventilation is proven to improve quality of life in patients with neuromuscular and chest wall disease and even mortality in a subgroup of patients. Recently updated Cochrane reviews [59, 68, 69] assessed 10 studies involving 173 patients with extrathoracic lung disease on chronic non-invasive ventilation. The review concluded that there is a consistent finding of improved quality of life with non-invasive ventilation. There was also less mortality in the subgroup of patients with motor neurone disease and Duchenne muscular dystrophy[47, 56]. One study by Raphael et al. [192], evaluated the use of nasal intermittent positive-pressure ventilation (NIPPV) in 70 young patients with Duchenne muscular dystrophy (DMD) without chronic respiratory failure. The patients were randomised to receive either conventional treatment alone (control group) or conventional treatment plus non-invasive positive-pressure ventilation (NIPPV group) in the form of volume-cycled ventilation for at least six hours per night as 10 ml per kilogram tidal volume. The aim of the study was to assess whether early NIPPV can limit the progression of restrictive lung disease and possibly improve survival. The study was stopped early due to increased mortality in the NIPPV group when compared to the control group (eight deaths versus two respectively). The study design and methodology are different from current practice

guidelines which may explain the increased mortality in the intervention group. Firstly, the participants were patients without respiratory failure with no criteria to start on non-invasive ventilation. Secondly, volume-cycled ventilation was used at a relatively high tidal volume (10ml/kg) in patients with no indication to start on ventilation. Thirdly, most of the deaths occurred due to retention of trachea-bronchial secretions at home; which implies that appropriate care of the ventilated patient was not adequate or that appropriate training was not provided to patients or carers.

Although the overall evidence for improved survival with the use of NIV in patients with extrathoracic restrictive lung disease appears relatively weak, this may be due to the paucity of randomised controlled studies, rather than necessarily a lack of clinical benefit.

A number of separate studies have assessed measures of physiological improvement and quality of life. The studies showed better parameters of gas exchange including better oxygenation and reduction in daytime hypercapnia. There was also improved sleep efficiency, sleep architecture with reduction in the apnoea hypopnoea index (AHI). Day time performance and psychosocial function also improved after ventilation. [51, 156, 160, 166, 182, 193].

### **1.11.7 Triggering of non-invasive ventilation**

Triggering of the ventilator is defined as “a patient’s spontaneous effort at initiating a breath followed by a mechanical response from the ventilator” [10]. It is a complex and interactive process between the patient and ventilator, that involves a number of variables. It is not only determined by the ventilator settings, but also by patient characteristics, including their physiological reserve. Triggering of a mechanically delivered breath depends on the type of inbuilt trigger mechanism in the ventilator,

which may be due to a pressure drop in the circuit due to the patient effort or a change in airway flow [10].

Appropriate triggering of mechanical ventilation is important not only in establishing effective ventilation, but also to ensure good patient-ventilator synchrony, patient comfort and adherence with treatment. This can be particularly problematic if the patient has underlying muscle weakness due to neuromuscular disease [42, 194]. Ineffective efforts are reasonably common and account for most events of patient-ventilator asynchrony [195].

In general, asynchrony can be divided into:

- 1- Ineffective triggering or effort (a patient's attempt at initiating a breath not followed by a ventilator delivered one)
- 2- Double triggering (the occurrence of two consecutive ventilatory cycles separated by very short expiratory time  $< \frac{1}{2}$  the mean inspiratory time)
- 3- Autotriggering or autocycling (the occurrence of three rapid successions of pressurizations at a respiratory rate  $>40$  breaths/minute and clearly above the patient's intrinsic respiratory rate)[169]
- 4- Premature cycling (premature change from inspiration to expiration)
- 5- Delayed cycling (delayed change from inspiration to expiration)

To assess dys-synchrony and ineffective efforts during nocturnal non-invasive ventilation in an outpatient setting polysomnography is required; however, a standard level one study (full polysomnography without special monitoring for ventilatory failure) will not be adequate.

Standard polysomnography (described under methods, chapter 2.2.41) may not identify respiratory effort in the chest and abdominal respiratory bands, nor in the diaphragm or chin electromyography (EMG). Adequate assessment of the presence or absence of

respiratory effort requires additional procedures. The most validated method is through the insertion of an oesophageal balloon which reflects changes in the pleural pressure. The pressure inside the pleural cavity is generally a negative pressure of -5 to -10 mmHg. The oesophageal balloon, when placed correctly, should reflect this negative pressure. When the patient takes a breath a more negative deflection in the balloon pressure is seen. While on a ventilator if such negative deflection is not followed by a machine breath; this can be labelled as an ineffective (or wasted) effort. If repeated the process is labelled ineffective triggering.

Double triggering and autotriggering can happen for a variety of reasons; the commonest of which relates to the timing of inspiration and expiration on the ventilator that does not match the patient's own. Other common causes include leak through the patient mask interface as well as inappropriate setting of triggering sensitivity on the ventilator. If the sensitivity is set too high (easy triggering) this can result in multiple breaths being mechanically delivered with minimal patient effort. The opposite is seen with lower sensitivity setting on the ventilator; which can make it harder for the patient to trigger; hence leading to more wasted effort.

Premature and delayed cycling can happen for similar reasons to the ones stated above including leak, maladjustment of inspiratory and expiratory times on the ventilator and upper airway obstruction [196].

There have not been many studies in the literature that assess optimal triggering of non-invasive ventilation. Many of the existing studies included a heterogeneous group of patients including those with COPD, where there are other factors such as the presence of intrinsic positive end expiratory pressure (PEEPi) that can affect triggering.

One study by Vignaux assessed ineffective efforts and patient-ventilator dys-synchrony in patients admitted with acute respiratory failure and treated with non-invasive

ventilation acutely in an ICU setting. The study was an observational study and non-randomised without the use of an oesophageal balloon to assess synchrony between the patient's respiratory efforts and ventilator delivered breaths. Leak was the commonest cause of dys-synchrony [197].

In a study by Carlucci et al., 69 patients with chronic respiratory failure were monitored during daytime before and after non-invasive ventilation for 60 minutes. The patient population was heterogeneous, with 45% having COPD and 55% having extrathoracic restrictive lung disease (44% CWD and 11% NMD). Asynchrony was only monitored for the last 15 minutes on ventilation via a gastro-oesophageal balloon and a pneumotachograph. Asynchrony was found in 58% of the patients with ineffective efforts as the predominant cause (45%). There was no significant difference between the two groups of patients whether the underlying pathology was an obstructive or a restrictive pattern. There was also no correlation with respiratory mechanics in those patients with a high asynchrony index (AI) versus those with a low one [195]. Another study demonstrated that ineffective triggering and asynchrony are associated with prolonged duration of ventilation in an intensive care setting [188].

Two Italian studies evaluated triggering and ineffective efforts in neuromuscular disease. Fanfulla and colleagues randomised nine chronically ventilated patients with neuromuscular disease to usual settings, titrated on simple clinical parameters, and physiological settings based on the patient's respiratory effort. This was measured by recording the patient's inspiratory muscle effort and required the insertion of an oesophageal balloon. The physiological arm had significantly improved gas exchange and sleep efficiency due to lack of ineffective efforts. The authors in their analysis concluded that an incorrect titration of inspiratory support or extrinsic PEEP may impede the trigger of the mechanical breath [135]. The second study that evaluated

patients with neuromuscular disease was by Crescimanno et al., where 18 patients were monitored for patient-ventilator asynchronies (PVA) and the effect on sleep structure both in hospital and at home. The patients had their ventilation optimised in hospital after undergoing nocturnal polygraphy and were monitored for PVA. At home, the patients underwent standard polysomnography with the addition of three additional electroencephalogram (EEG) channels to the other channels monitored during the in-hospital polygraphy. The patient-ventilator asynchrony index was assessed from the polygraphy and polysomnography traces without the insertion of an oesophageal balloon. The results were compared between hospital and home environments and included ineffective efforts, autotriggering, prolonged insufflations and patient-ventilator asynchrony index as a summation of all. The asynchrony index and autotriggering appeared to be higher at home than in hospital which may be related to the fact that patients had higher leak in the home environment. Ineffective efforts and prolonged insufflation indices were not different [198].

Triggering of the ventilator by the patient can be either a pressure-trigger where the patient has to generate negative pressure that is sensed by the ventilator to deliver an assisted breath or a flow-trigger where the ventilator's flow sensor detects a variation in flow by the patient and develops the assisted breath. New algorithms of triggering ventilators have emerged combining multiple mechanisms. In addition to assisted breaths, the ventilator can deliver mandatory breaths that are not triggered by the patient, often referred to as backup respiratory rate (BURR) [199].

As can be appreciated, triggering of the ventilator for an assisted breath relies on the patient's ability to fulfil the trigger requirements, whether it is generating enough variation in flow or negative pressure. This can be problematic particularly in neuromuscular disease, where reduced muscle strength is the underlying mechanism in

causing respiratory failure. It can be easily postulated that having the patient on a purely spontaneous mode may lead to ineffective efforts and failure to trigger the ventilator. This may have negative effects on nocturnal gas exchange, quality of sleep and daytime function.

For this reason, some centres find it more attractive to use modes of ventilation that have a backup rate such as ST mode to avoid failure of the patient triggering the ventilator.

### **1.11.8 Spontaneous versus spontaneous timed mode of ventilation**

So far there has been little research comparing spontaneous and spontaneous timed modes clinically. In a small study by Contal et al., 10 patients with obesity hypoventilation syndrome were randomly implemented on three different settings of non-invasive ventilation for three consecutive nights. On one night the participants had no back up respiratory rate with the ventilator in spontaneous mode. The other two nights were randomly assigned either a low back up respiratory rate or a high back up respiratory rate. The participants were monitored with polysomnography and transcutaneous CO<sub>2</sub> monitoring to assess for sleep architecture and respiratory events. The results of the study showed that the spontaneous mode was associated with a higher rate of respiratory events, mainly mixed and central apnoeas, and a higher oxygen desaturation index (ODI). However, overall, there was no significant effect on sleep quality [200].

In another study by Restrickett et al., 12 patients were randomly assigned for one night on either nasal intermittent positive pressure ventilation (NIPPV), which incorporates a preset minimum respiratory rate, or nasal positive pressure ventilation (NPPV) in the form of pressure support only with no preset respiratory rate, after a control night with

no ventilatory support. Five patients had chronic airflow obstruction and seven patients had extrathoracic lung restriction from either neuromuscular disease or chest wall disease. The study mainly assessed ventilation parameters as well as a visual analogue score assessing sleep quality and overall comfort in comparison to the control night. There was significant improvement in oxygenation and drop in transcutaneous CO<sub>2</sub> levels with both modes of ventilation in comparison to the control night. There was no significant difference between the two modes of non-invasive ventilation themselves in improvement of ventilation parameters. There was also no difference between the two modes in sleep quality or overall comfort [201].

There are potential problems in either spontaneous or spontaneous timed mode that can lead to poor quality sleep [169], which can potentially cause impaired psychomotor functional ability and performance[202].

In Australia, it is estimated that 95 % of patients on home non-invasive ventilation are using pressure cycled ventilation. Of those, 43% receive ventilation in spontaneous mode, and 56% receive spontaneous timed mode, with very little data to compare the two modes directly. The mean inspiratory pressure (IPAP) used is 17.5 (16.0–19.3) cm H<sub>2</sub>O, and the mean expiratory pressure (EPAP) is 8.9 (8.0–9.2) cm H<sub>2</sub>O. The mean backup rate for spontaneous timed mode is 15.8(±2.5) breaths/min[174].

**In summary**, whilst pressure cycled ventilation is the commonest mode of ventilation used worldwide including Australia, there are no evidence-based guidelines or data to suggest which mode of pressure cycling is better spontaneous or spontaneous timed. Practices differ between respiratory units and seem to be roughly equally divided between the two modes, although spontaneous timed mode is slightly more utilised. Some guidelines imply that using spontaneous timed mode, with a breath rate matching that of the patient, should be routinely used, particularly if there is concern about the patient not have enough respiratory drive, but this is largely based on non-randomised studies specifically comparing the two modes or expert opinion rather than evidence [153, 154]. It is perceived that spontaneous timed mode may be superior in achieving adequate ventilation and being associated with fewer ineffective efforts; however, this is not proven.

As there is current clinical equipoise in the literature as to which mode of ventilation is superior[182], there is a need for a clinical study to assess both modes head to head in a double-blind design. It is essential to compare the two directly in a homogeneous group with slowly progressive chronic respiratory failure such as those with extrathoracic lung restriction patients. The study design should assess correction of hypoventilation including PCO<sub>2</sub> measurements and oxygenation. It should also assess the impact on the patient such as sleep quality and efficiency, psychomotor skills as well as patient preference. This was the aim in this thesis.

## **Chapter 2: Study 1 “Spontaneous Versus Spontaneous Timed assisted ventilation in patients with extra-thoracic restrictive lung disease”**

### **2.1 Introduction**

Assisted ventilation at home, usually via a mask, can stabilise ventilatory failure, reduce mortality and improve quality of life[47, 56, 59, 156, 193]. The Victorian respiratory support service (VRSS) at Austin Health is the state-wide service for provision of home ventilation in the state of Victoria, Australia. The service accepts referrals for a number of conditions requiring long-term home mechanical ventilation. This includes patients with neuromuscular disease, chest wall disease, obesity hypoventilation syndrome and chronic obstructive pulmonary disease. By far the commonest referrals are for patients with neuromuscular disease, in particular, motor neurone disease.

A variety of ventilation modes have been described in the treatment of the range of conditions requiring home ventilatory support in Victoria. Bi-level pressure support ventilation is most common and is usually delivered using either a spontaneous mode of ventilation (S), where the patient’s breath must trigger the ventilator, or a spontaneous timed mode of ventilation (ST), where the ventilator provides a minimum set breath rate to attempt to avoid a low patient breath rate resulting in hypoventilation. The ST mode usually also allows the patient to trigger the ventilator if needed; hence the descriptor “spontaneous timed”. There is also a “timed mode” which is rarely used, as it does not allow spontaneous breathing in addition to mechanically delivered breaths. There are advantages and disadvantages associated with both of these ventilatory modes. For example, the spontaneous

mode if triggered correctly should be completely synchronous with the patient's own breathing and hence potentially most comfortable. However, occasionally there is failure of triggering, resulting in under-ventilation and increased ventilatory failure. Other issues include failure of cycling to expiration that can result in dyssynchrony between the patient and ventilator breaths, increased leak and ineffective ventilation. All of these issues can impair ventilation, disturb patients' sleep and cause discomfort.

A spontaneous timed mode may reduce failure to trigger and cycle and the risk of central respiratory events, enhancing ventilation; if the settings were set appropriately to match the patient condition and breathing pattern; however, it may not be synchronous with the patient's own ventilation and may also result in over-ventilation.

There is no current evidence that one mode of ventilation is superior to the other in extrathoracic lung restriction resulting from neuromuscular and chest wall disease.

**The aim of the study in this thesis was to compare the two methods of ventilation in 20 patients with kyphoscoliosis and stable neuromuscular disease in a cross over design. The main objective was to assess adequacy of ventilation and quality of sleep as assessed by a sleep study. Other objectives included the subjects' perception of sleep and breathing comfort, in addition to measures of sleepiness and psychomotor function. The null hypothesis was that there was no difference between the two modes in the primary or secondary endpoints.**

The study was approved by the Austin Health Research Ethics Committee and registered with what was then called the Australian clinical trials registry (ACTR), trial no 82620. The trial was subsequently registered under the Australian New Zealand clinical trials registry (ANZCTR), trial no 12608000103369.

## **2.2 Methods**

### **2.2.1 Study population**

The participants were clinically stable patients with extra-thoracic restrictive lung disease who were receiving long term non-invasive ventilation for type two respiratory failure. Stability was defined as being on non-invasive ventilation for three months or more.

There were a number of reasons why stable patients rather than new patients naïve to non-invasive ventilation (NIV) were selected for the study. Firstly, patients may take weeks to adapt to non-invasive ventilation or they may not be adherent to therapy. In this study by Vitacca et al., 213 subjects with amyotrophic lateral sclerosis were followed up for a period of 36 months across three sites. The patients were divided into an early implementation group to adapt to non-invasive ventilation and a late group. Out of the total subjects, 167 patients failed NIV after 36 months of follow up, with 50% failing in the first year in the late group and 10% in the early adaptation group [203]. As the number of studies to assess adaptation to therapy in non-invasive ventilation is limited, a review of the literature involving continuous positive airway pressure (CPAP), another form of positive pressure treatment using a relatively similar interface, in patients with sleep apnoea, is helpful. In this study by Weaver et al., who assessed CPAP usage in the first 9 weeks of treatment, approximately half the patients skipped CPAP therapy between one to seven days per week and also had great variability in the number of hours used per night when they did, in fact, use it [204]. For these reasons, it would have been potentially difficult for the participants in the first few weeks while they were still adapting to this new therapy to comply with treatment, which would have compromised the study.

Secondly, as new patients, they would have had to come off ventilation during the washout period, which would have proved ethically challenging, given their newly diagnosed respiratory failure. The study, therefore, may have not received ethics approval, as the relatively long washout period of two weeks may have been considered a denial of life-saving treatment. It would not have been possible to give the participants one of the two modes tested in this study during the washout period, as this would have caused bias towards one of the modes as the patient was adapting to ventilation.

Thirdly, the recruitment for the study would have been quite difficult and it would have taken a very long time to enrol the desired number of participants. For a single centre study, the number of new referrals per year for ventilation related to chest wall disease or stable neuromuscular disease is limited. In our centre, approximately a total of 250 referrals are received for long term ventilation, the majority of whom are related to other conditions such as motor neurone disease (MND). This also includes other conditions such as obesity hypoventilation syndrome (OHS) and chronic obstructive pulmonary disease (COPD, both of which were excluded from the study.

When reviewing the relevant literature, patients stabilised on long term ventilation were generally similarly chosen for study. In the study by Restrick et al., which compared two modes of ventilation, the authors explained that “patients with established respiratory failure on non-invasive ventilation were chosen since the purpose of the study was to compare two modes of ventilation and those patients were accustomed to NIV already” [201]. In the study by Fanfulla and colleagues, which aimed to study two different settings of ventilation, one physiological and the other usual setting, patients selected for the study were, again, those with established chronic respiratory failure who were already treated with home non-invasive ventilation [135]. A similar rationale was also adopted in studies comparing ventilatory modes in patients with (OHS). Whilst

these patients have different physiology to our cohort, the studies that addressed different modes of ventilation would have had a similar concept. In the study by Contal et al., they studied the effect of a backup respiratory rate (BURR); either low or high; versus spontaneous mode in patients with stable obesity hypoventilation syndrome already established on non-invasive positive pressure ventilation (NPPV) [205].

For all the above reasons, it was more practical to choose patients with chronic stable extra-thoracic lung disease.

The participants were all patients of the Victorian respiratory support service, identified from its database. Most patients in the study had kyphoscoliosis except for two patients who had myopathy.

Exclusion criteria for this study were:

- Chronic obstructive lung disease
- Progressive neuromuscular disease (such (MND)
- The presence of a tracheostomy in situ
- Age less than 18 years or more than 80 years
- Being unable to obtain informed consent.

### **2.2.2 Enrolment**

Potential participants were identified from the Victorian Respiratory Support Service database and from the outpatient clinic.

Once it was established that the participant was eligible for the study, he or she was contacted by the principal investigator to explain the study. Patients were contacted by telephone, or face to face approach took place. A full explanation of the study was provided to the potential participant by the principal investigator. The information provided ensured there was no bias towards either mode of ventilation. The investigator

explained the concept of clinical equipoise and that it applied to these two modes of bilevel ventilatory support.

The participant was then sent or given the Patient Information and Consent Form (PICF) before enrolment was finalised. An appointment was made with the investigator to answer questions, obtain written informed consent and organise study dates. The study was conducted from August 2008 with all participants completing the randomisation by the end of November 2013.

### **2.2.3 Blinding and randomisation**

Once the participant was enrolled in the study, he or she was allocated a random order of ventilation treatment through a computer-generated program “Research Randomizer”. An unblinded staff member at the centre had access to this computer program and was responsible for randomisation. They also filled out the sleep study information request which ensured that the mode of ventilation was not stated. The respiratory rate, in particular, was left blank in the request form, with either of the two modes allocated. The same staff member implemented the participant on the allocated mode in the morning after undergoing the pre-study tests and the overnight polysomnography as described below in the study protocol (figure 2.1). This unblinded staff member did not participate in data analysis.

The overnight sleep scientist who supervised the participants during their polysomnography had no access to the ventilation mode allocated which was not stated anywhere. They were also not allowed to look at the settings on the actual ventilator. They were instructed not to make any entries in the polysomnography software that could in any way compromise the blinding process.

Analysis of the sleep studies for staging and scoring was performed by a blinded sleep scientist who had no access to the randomisation program or ventilation mode allocation on the sleep study information sheet. It was ensured that there were no entries by the overnight sleep scientist in the polysomnography software to unblind the scoring scientist. The scientist was not involved in any data analysis.

## **2.2.4 Study Protocol**

### **2.2.4.1 Initial calibration and safety procedure study**

Following enrolment and randomisation, the participant attended the sleep laboratory in the afternoon and stayed overnight for the first sleep study. The first sleep study was always conducted in spontaneous mode to ensure the settings were safe and adequate for all patients; who were all new to this mode. The participants were not aware that this was spontaneous mode but rather informed that the ventilator settings were different to their own. It was also explained that the first sleep study was to ensure safety and suitability of them participating in this study on a different mode of ventilation.

No participants in this project were on spontaneous mode as their normal mode of ventilation at home; however, this was not an exclusion criterion. The ventilator used was a “Resmed VPAP III ST-A” which is capable of delivering both types of ventilation to maximum pressures as required.

The settings for the initial calibration and safety study were all performed by the principal investigator. If the participant’s usual settings were on spontaneous timed pressure cycled ventilation, the backup respiratory rate was changed to zero to convert to spontaneous mode ventilation; however, no changes to the inspiratory (IPAP), expiratory (EPAP) pressures, were made. The minimum and maximum inspiratory

times (TiMin & TiMax) were set at 0.1 and 4 seconds respectively to allow maximum spontaneous free breathing for the patient in this mode. Trigger and cycle were set to medium as per standard common settings for this type of bilevel machine.

If the participant was on volume cycled ventilator, the tidal volume and machine set respiratory rate were recorded. The patient was then implemented on spontaneous pressure cycled mode for the initial calibration and safety procedure study. The EPAP was set at a minimum pressure of 4 and a pressure support (PS = IPAP - EPAP) value that achieved a similar tidal volume to his/her original tidal volume on their volume cycled ventilator. The TiMin & TiMax were set between 0.1 and 4 seconds as above. The masks were changed to vented masks to suit pressure cycled ventilation.

Settings were allowed to be changed overnight by the sleep scientist as per appendix 4; however, if they had any safety concerns, the principal investigator was contacted to give advice. The patient was reviewed in the morning by the principal investigator prior to randomisation to ensure safety of this mode and to address any concerns by the participant.

A standard sleep study as per the VRSS protocol was conducted to assess sleep and ventilation parameters. Signals recorded included electroencephalograph (EEG), electro-cardiograph (ECG), chin electro-myograph (EMG), electro-oculograph (EOG) for eye movement, oxygen saturation (SpO<sub>2</sub>), transcutaneous CO<sub>2</sub> (PtcCO<sub>2</sub>), mask pressure, flow signal, thoracic and abdominal respiratory inductance plethysmography (RIP), diaphragm electromyograph (dEMG), position monitoring, limb EMG, snore sensor as well as audio and visual monitoring. Standard calibration of the sleep study equipment and sensors function was performed by the sleep scientist prior to proceeding with the study as per standard ventilation study protocol at our institution. The principal

investigator was in attendance during setup of the sleep study; prior to randomisation; to ensure the protocol was followed accurately.

#### **2.2.4.2 Allocation of ventilation modes for the research project**

The study was a randomised cross over design with two weeks on each mode and a two-week washout period in between. The two-period cycle was chosen as it was anticipated that there may be difficulty in participant recruitment for a single centre study with a limited number of referrals per year of approximately 250 new patients, most of whom have other conditions (such as MND), that were excluded in this study. After the overnight initial calibration and safety procedure sleep study on spontaneous mode, the principal investigator reviewed the patient in the morning to ensure they were able to tolerate the new mode without any significant difficulty. The principal investigator also reviewed the sleep study and if it was deemed safe to proceed on the current ventilator settings with no obvious severe hypoventilation (e.g. rise in transcutaneous CO<sub>2</sub> > 10mmHg from baseline, or persistent absolute values above 60mmHg, SpO<sub>2</sub> < 85% for 50% of the study time) (appendix 4), the participant then proceeded with the randomisation by the un-blinded staff member who then allocated the participant to one of the arms, according to the computer-generated program. The participant was blinded to the mode of ventilation allocated. If the participant required a change of mask, this was fitted as needed by the unblinded staff member but could not be changed again afterwards to ensure standardisation of procedures for the entire study period.

The settings for S mode and ST mode were identical in the inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). The settings were also similar in the trigger and cycling, both being medium as per the standard default settings

for these modes. There were two main differences between S mode and ST mode. The first being the absence of backup respiratory rate (BURR), if the patient was randomised to S mode which was set to zero. If the patient was randomised to ST mode, the setting was either left as per their own previous backup rate, if they were previously on ST mode (as this was considered their optimal backup rate), or set just below their intrinsic respiratory rate off ventilation, if they were previously volume-cycled ventilation.

The second difference in settings was that of minimum inspiratory time and maximum inspiratory time. As described above, in S mode the TiMin was set at 0.1 seconds and the TiMax was set at 4 seconds to allow maximum free breathing for the participant on this mode. In ST mode the TiMin and TiMax were set between 0.5 and 1.6 seconds respectively as per usual settings in the study centre, depending on patient comfort and tidal volumes achieved.

Below is a table describing a summary of the difference in settings between the two modes.

Parameter setting	Spontaneous Mode	Spontaneous Timed Mode
Backup RR	0	As per previous settings or just below the participant's intrinsic RR
IPAP & EPAP	Identical to ST mode	Identical to S Mode
TiMin & TiMax	0.1 – 4 sec	As per previous settings or between 0.5 – 1.6 sec
Trigger	Medium	Medium
Cycle	Medium	Medium

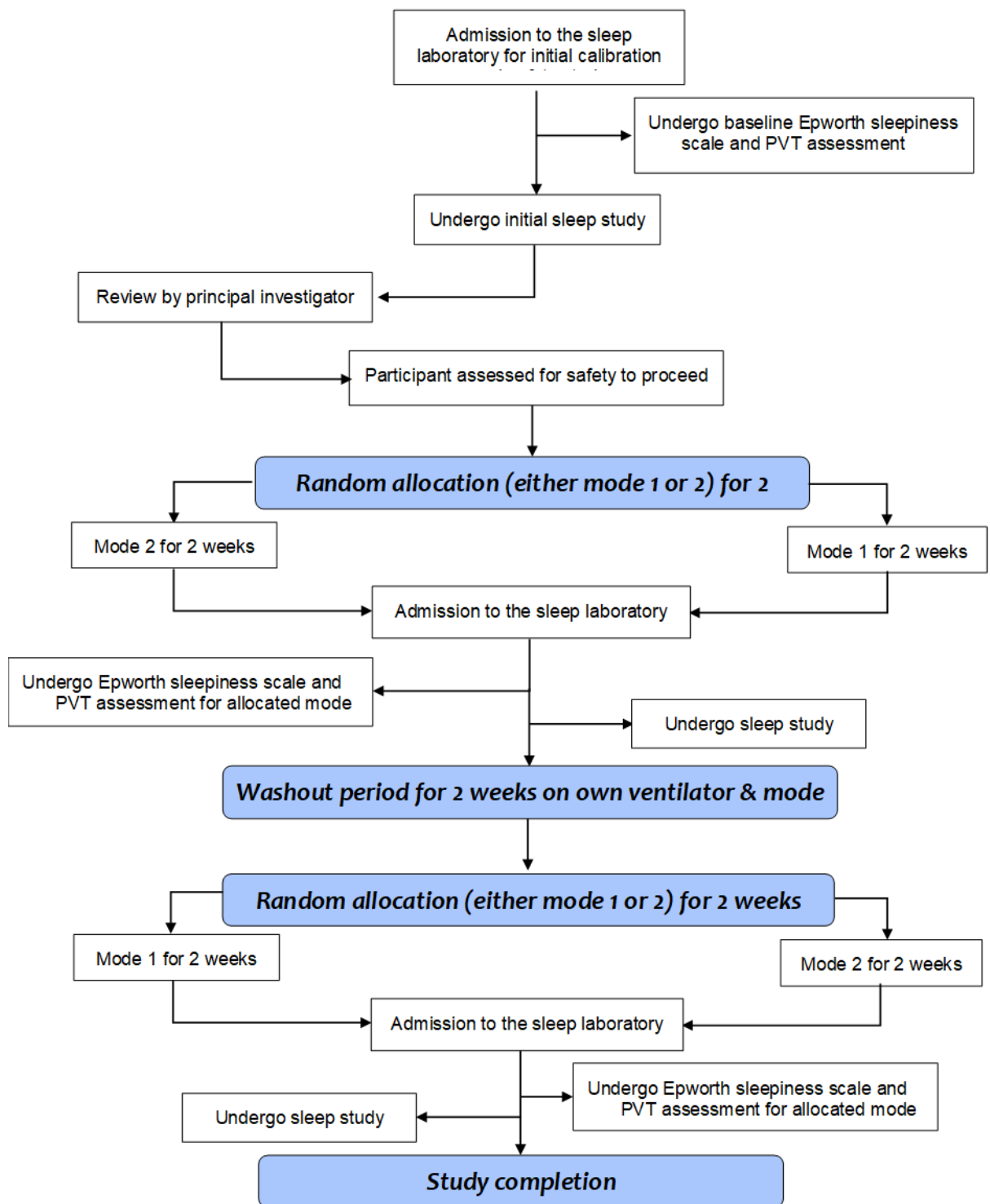
Table 2.1 Summary of difference in settings between S mode and ST mode

RR = respiratory rate, sec = seconds

Once the participant was allocated the study mode by the unblinded staff member, he or she was discharged home on a loan ventilator with the allocated settings for the first mode for a period of two weeks. The participant then returned back to the sleep laboratory at the end of the two weeks in the afternoon to have a sleep study to collect the data on this mode. The participant was then asked to fill out a bespoke questionnaire targeted towards overall comfort on the ventilator, sleep quality and daytime activity (Appendix 2). The participant also filled out the Epworth sleepiness scale (ESS) for assessment of sleepiness. He/she underwent a neuro-behavioural assessment using a psychomotor vigilance test (PVT).

The un-blinded staff member then allocated the participant to the second mode of ventilation and programmed the ventilator to the new mode prior to the participant's discharge home. The participant was instructed to use their usual ventilator and mode

of ventilation for two weeks to complete the washout period before starting on the second mode as already programmed on the loan ventilator. The two week washout period was determined based on previous studies with similar design [172]. The participant remained on the second mode for a further two weeks before returning for the third and final sleep study. Again, they went through the same procedure as described above post completion of the first mode. The total cycle of participant involvement in the study was six weeks inclusive of two weeks on each mode of ventilation and two weeks washout period (figure 2.1). The study protocol technical sheet is displayed in (Appendix 3).



**Figure 2.1: Diagram of study design**

## **2.2.5 Laboratory procedures post randomisation**

The participant was admitted to the sleep laboratory in the afternoon prior to the sleep study after each mode, where the procedure, including questionnaires, was explained in detail by the principal investigator. Prior to conducting the sleep study, the patient filled out two questionnaires. “The Epworth Sleepiness Scale” is a validated questionnaire, used routinely in the assessment of sleep disordered breathing, which assesses the degree of daytime sleepiness [112] (Appendix 1). The second questionnaire was bespoke and designed to assess the patient’s assessment of his/her experience with each mode of ventilation with reference to his/her normal mode of ventilation. The following sections explain the procedure for the sleep study, conduction of the questionnaires and psychomotor vigilance testing.

### **2.2.5.1 Sleep Study procedures**

The participants underwent a sleep study while undergoing the initial calibration and safety study and after each allocated mode of ventilation. The participants were admitted to the dedicated sleep laboratory for non-invasive ventilation studies, where assistance by nursing staff is available if required, to assess the impact of each mode on ventilation and sleep. A level one polysomnography study was performed as per standard protocol for non-invasive ventilation on each mode. Additional diaphragm EMG (d-EMG) to assess the presence or absence of diaphragm activity in order to assist in determining patient effort and transcutaneous CO<sub>2</sub> (PtcCO<sub>2</sub>) monitoring to assess CO<sub>2</sub> trends overnight as a measure of hypoventilation. The software used was Compumedics E-series equipment and PSG3 software. The standard channels for a level one polysomnogram include electro-encephalography (EEG) to stage sleep and wake periods, ocular movements (EOG) to assess sleep particularly rapid eye

movement sleep (REM), electromyography (EMG) to assess for muscle tone and activity, electrocardiography (ECG) to assess cardiac rhythm and heart rate variability during sleep, thoracic and abdominal movement through Respiratory Inductance Plethysmography bands (RIP) to assess for participant effort and direction of muscle movement, oxygen saturation monitoring (SpO<sub>2</sub>) sampled at one hertz (Model: Radiometer Oximeter) as a measure of scoring respiratory events and assessing hypoventilation, pressure signal from the ventilator mask (P<sub>mask</sub>) to assess contour and pressure achieved by the ventilator, flow signal derived from mask pressure (Flow-VPAP) to assess adequacy of flow based on contour, leak signal (Leak-VPAP) to assess and quantify the presence or absence of leak, position sensor (Pos) to determine supine versus non-supine sleep, leg movement electromyography (Leg-R & Leg-L) to assess for restless legs and periodic limb movement of sleep, snoring microphone (snore) and light or darkness trace (light) to determine sleep latency. Arterial blood gases are taken in the evening off ventilation and in the early morning after cessation of ventilation.

The sleep studies were conducted according to a specified protocol particular for the study with no changes made to ventilator settings overnight. It followed the general guidelines for a standard non-invasive ventilation sleep study according to the local institution protocol as well as Australian guidelines, in addition to the specified requirement for the study (Appendix 3). The sleep study software used was “Compumedics Profusion 3”.

The primary investigator, who was blinded to the mode of ventilation, attended the initial part of the study to conduct the initial psychomotor vigilance testing and collect non-sleep study data and questionnaires according to the protocol. The primary investigator also attended in the morning prior to participant discharge home to explain the next procedures and ensure follow up of protocol.

Once all the participants were enrolled and studies were completed, the sleep studies were stored in a specific drive on the network accessible only to the department. A dedicated blinded sleep scientist was responsible for the primary analysis of the sleep studies according to set criteria as per the American Academy of Sleep Medicine (AASM) 1st edition [206]. A second blinded scientist did a separate analysis of some of the studies and a concordance analysis was performed to ensure agreement on the interpretation of signals and results.

Sleep was divided into Non-Rapid Eye Movement (NREM) and classified into NREM 1, NREM 2, NREM 3 and Rapid Eye Movement (REM) phases. Although statistics were done for each individual phase of sleep, only the total sleep per phase is displayed below (NREMTotal\_A, NREM total\_B or REMTotal\_A and REMTotal\_B). The position was labelled as supine (Sup) and non-supine (NonSup). Measures included sleep efficiency; defined as percentage of total sleep time in relation to total time in bed (SlpEff\_A or SlpEff\_B), total sleep time, awakenings and wake time.

A troubleshooting sheet was provided for the scientists conducting the study (Appendix 4), and in addition, the principal investigator was available on call for any troubleshooting overnight.

Each participant was reviewed by the principal investigator in the morning following the sleep study to ensure the protocol was followed. The participant was then discharged on the appropriate setting as per protocol by the unblinded staff member.

### 2.2.5.2 Psychomotor Vigilance Task (PVT)

On the night of admission prior to the sleep study, the patient was asked to perform a PVT as a measure of psychomotor performance[131]. The test was conducted in a quiet room with no interruption to maximise concentration. The test procedure involves pressing a button after a randomly timed light appearing at different intervals. The light shows the time lapsed until the button is pressed. The study name and patient number and details are entered into the device. It can also be adjusted for right and left-handedness. The test is conducted over ten minutes after a practice of one minute which can be repeated if required.

Three tests were performed. The first at baseline, prior to randomisation, the second after the first mode of ventilation and the third test after the second mode of ventilation. Data from each PVT were downloaded by the program “PVTcomm” and analysed by the dedicated software “PVT React”. Of the various measurements taken, the main results of interest taken were mean reaction time expressed in milliseconds (msec) and the number of lapses (defined as missing to press the button after 500 milliseconds). The values were compared to the baseline psychomotor vigilance test results. The PVT box is illustrated below (figure 2.6)



**Figure 2.2: PVT Box**

### **2.2.6 Epworth sleepiness scale (ESS)**

Participants were asked to fill out the Epworth sleepiness scale three times during the period of the study, before undergoing their polysomnography (Appendix 1). The first questionnaire was undertaken as a baseline before randomisation on the night of the initial calibration and safety study, and then again after the two-week treatment period on each ventilation mode prior to the corresponding sleep study. The participants filled out the questionnaire in the evening of the sleep study prior to the polysomnography. The completed questionnaire was then collected by the principal investigator and stored securely.

### **2.2.7 Patient preference**

Participants completed a questionnaire after each mode of ventilation to assess their level of comfort and preference with regards to the allocated mode. The questionnaire was filled in the evening prior to the sleep study for the allocated mode. The questionnaire involved an assessment of breathing comfort, level of energy, whether they are feeling refreshed in the morning, the presence or absence of headaches and sleep quality as compared with their normal mode of ventilation. Each response was divided into 5 categories, either much worse, worse, no difference, better or much better and each response was given a grade of one to five respectively. An aggregate score was calculated as a sum of the individual responses per symptom.

The participants also filled out a questionnaire to compare the two modes directly for similar parameters as above (Appendix 2). It was explained to the participants prior to filling out the questionnaire that neither the principal investigator nor the patient knew what the allocated mode was. Every care was taken to ensure the absence of unblinding. The participants completed the questionnaire on their own while the primary

investigator left the room. The primary investigator then collected the completed questionnaire and stored it securely.

### **2.2.8 Endpoints**

#### **Primary outcome (in all patients):**

- 1- Correction of hypoventilation measured as the difference between evening (pre-ventilation) and morning (post-ventilation) PaCO<sub>2</sub>, and the day time PaCO<sub>2</sub> at the end of 2 weeks.
- 2- Degree of oxyhaemoglobin desaturation as assessed by the percentage of total sleep time below 90% and 85%. Also, the lowest value of oxyhaemoglobin desaturation during Non-Rapid Eye Movement sleep and Rapid Eye movement sleep.

#### **Secondary outcomes**

- 1- Sleep parameters as assessed by the number of respiratory events overnight [Apnoea Hypopnoea index (AHI)], arousals, total sleep time and sleep efficiency.
- 2- Impact of the ventilation mode on the participants as assessed by:
  - a. Epworth sleepiness scale score (ESS) as a measure of sleepiness
  - b. Psychomotor vigilance test (PVT) as a measure of performance
  - c. Questionnaire about patient preference with regards to the allocated mode of ventilation

### **2.2.9 Data collection and statistical analysis**

The primary investigator collected all data including patient demographics and previous ventilation settings. He also collected all non-sleep study data after

supervising the PVT testing and the questionnaires on all participants. All data were entered into excel sheets where the treatment arm was blinded by the allocated code. After analysis of the sleep studies by the dedicated scientist, the data was exported from the Compumedics software to a separate excel sheet. The data were then prepared for clean export into the statistical software by the principal investigator.

The study was designed to detect a 5 mmHg difference in PaCO<sub>2</sub> between the 2 groups with an expected standard deviation of 4 mmHg. Recruitment of twenty patients was required to have an 80% power to find such a difference at an alpha of 0.05. All data were analysed by using the software “IBM SPSS version 23”. Data were displayed as mean and standard deviation or median and range for parametric and non-parametric data respectively. Statistical significance was set at 0.05 for all analyses. A paired student t-test was used for continuous data with a normal distribution. For non-normally distributed data Wilcoxon Signed Rank Test was utilised. For nominal or categorical data ordinal regression analysis was used. All statistical analyses were performed by the principal investigator who was blinded to the mode of ventilation until analysis was completed.

## **Chapter 3**

### **3 Results of study 1 “spontaneous versus spontaneous timed mode of assisted ventilation in patients with extrathoracic restrictive lung disease”**

#### **3.1 Participants**

Patients of the Victorian respiratory support service on non-invasive ventilation were screened for their underlying cause of respiratory failure to assess suitability for the study. Patients with stable extra-thoracic lung restriction due to chest wall disease or neuromuscular disease were identified.

Apart from the exclusion criteria listed above in the methods section, the following categories of patients, who would have been eligible, were declined for the following reasons:

- Patients who lived outside the metropolitan area far from the study centre
- Non-English-speaking patients who had no adequate means to understand and consent to the study
- Patients with significant disability or frailty which would have affected their ability to attend the sleep laboratory three times in succession over a six-week period
- Patients who had visual impairment or significant arm weakness, which would prevent from performing the psychomotor vigilance test (PVT)

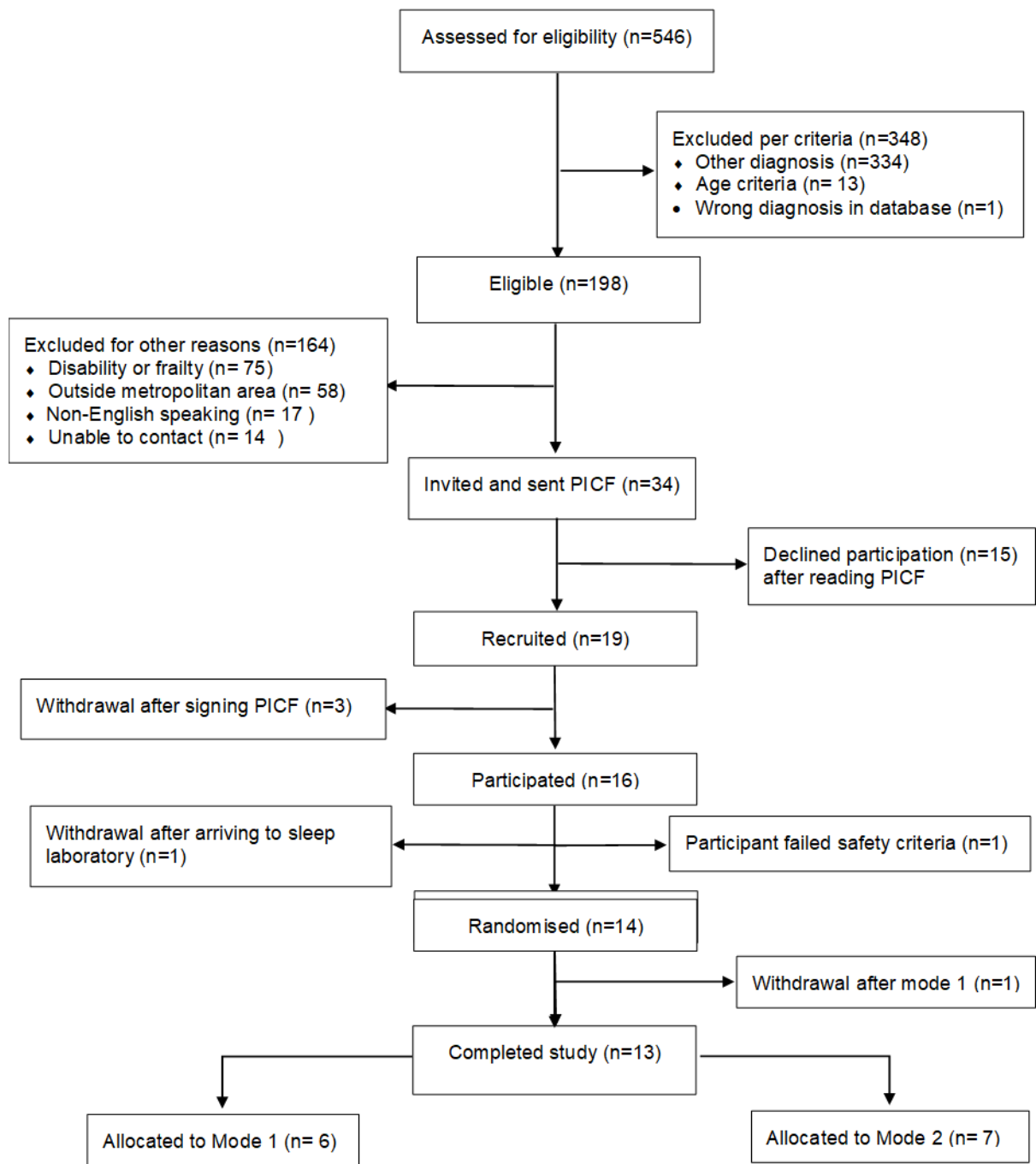
The desired number of 20 participants was not achieved due to a number of reasons. The first being that the potential participants had to be residents in the metropolitan suburbs rather than living in rural areas where travelling to the hospital sleep

laboratory three times in six weeks would have been difficult. The second main reason in difficulty with enrolment is that a lot of patients with extrathoracic restrictive lung disease are relatively frail due to their underlying medical condition; particularly those with neuromuscular disease. In fact, a majority of these patients do not drive, are in a wheelchair or need a carer providing help with most of their daily activities. For some participants a carer or a relative would have had to be available to drive them to hospital on each occasion they were undergoing each of the three sleep studies. Whilst some patients agreed in principle to participate in the study, a few refused to participate after reading the patient information and consent form (PICF) and hearing the details of the process involved.

Other reasons include fear about trying a different mode of ventilation or mask; particularly for those who were previously on volume cycled ventilation (VCV), and worry about following the protocol of changing modes of ventilation, going back on their own ventilator during the washout period and then returning back to the second mode of the ventilation in the trial. Some patients had visual impairment and difficulty using their arms, hence they would not have been able to do the psychomotor vigilance test. There were other individual reasons which made it difficult for potential patients to be recruited to the study.

Out of 546 patients screened through the database and outpatients department, a total of 198 patients seemed eligible to participate in the study after applying the exclusion criteria. After further review of the eligible patients' circumstances, 164 patients were further declined due to the reasons listed above, such as living outside the metropolitan area, having a language barrier or had a disability to prevent them from participating. A total 34 of patients were invited to undergo the study and were all sent the participant information and consent form (PICF). After reading the

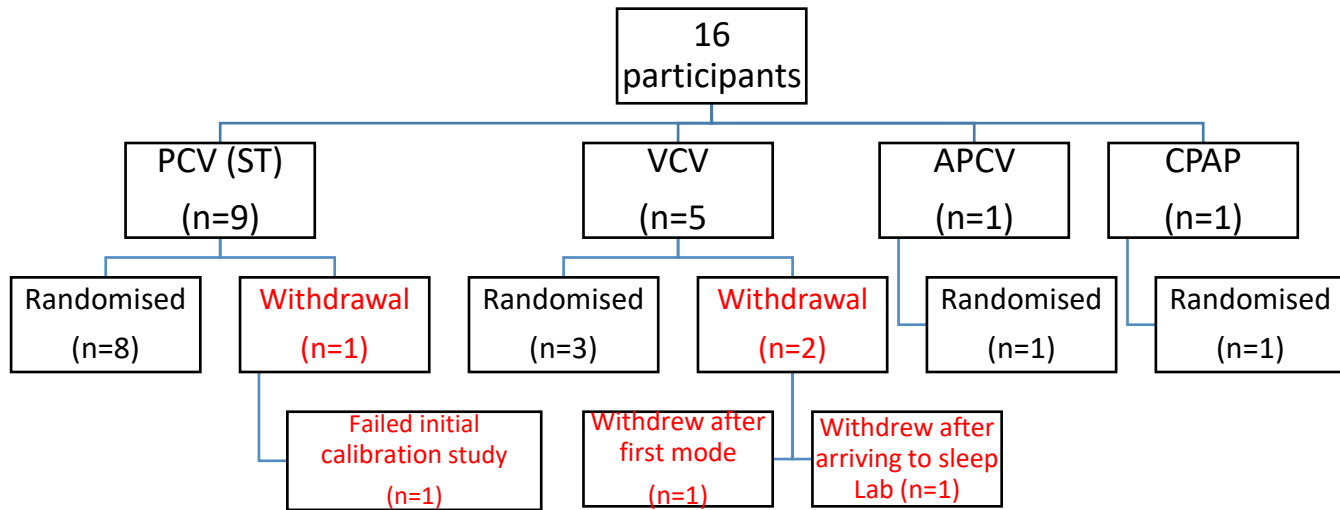
consent form, 15 patients declined to participate by telephone conversation. A total of 19 participants signed the patient information and consent form; however, three patients withdrew from the study afterwards as they felt they are unable to commit to the six-week cycle and/or attending the sleep laboratory three times. Out of the 16 participants who actually attend the hospital to start the study, one participant withdrew after arriving to the sleep laboratory for the initial calibration and safety study and changing their mind. One participant failed in the initial calibration and safety study and was not randomised, according to the troubleshooting and safety criteria, defined as persistent rise in transcutaneous CO<sub>2</sub> > 10mmHg from baseline, or persistent absolute values above 60mmHg or SpO<sub>2</sub> < 85% for 50% of the study time. A total of 14 participants were randomised; however, one participant withdrew after the first allocated mode, as they did not feel comfortable with the new mode. A final number of 13 participants completed the randomisation process. One patient completed both modes of the study but did not attend the sleep study after the second mode due to personal circumstances. He did complete the preference and ESS questionnaires (Appendix 2). An illustration of participant recruitment, withdrawal and exclusion is displayed below (figure 3.1).



**Figure 3.1 CONSORT Flow diagram of patient recruitment for the main study (study 1), PICF = patient informed consent form**

The patients recruited had moderate to severe lung restriction on lung function tests. The table below represents the patient demographics (Table 3.1)

Out of the 16 patients, two patients had neuromuscular disease (NMD) and the rest had kyphoscoliosis. One of the patients with NMD had facioscapulohumeral muscular dystrophy and had been on non-invasive ventilation for three years prior to enrolment in the study. The other patient with NMD had undifferentiated myopathy causing his extrathoracic lung restriction. He had been on non-invasive ventilation (NIV) for two years and eight months prior to enrolment in the study. Both these patients completed the randomisation process; however, the patient with facioscapulohumeral muscular dystrophy had to withdraw after completing the second mode and did not attend the last sleep study due to personal circumstances rather than due to his underlying condition. The remaining 14 patients had chest wall disease due to kyphoscoliosis and were on non-invasive ventilation for periods varying from 4 months to 14 years (mean  $5.5 \pm 4.9$  years). Out of the 14 participants with chest wall disease, 11 completed the study due to the reasons described above. Regarding the mode of ventilation used prior to the study, nine patients were on pressure cycled ventilation on spontaneous timed mode. Five patients were on volume cycled ventilation. One patient was on assist pressure control ventilation (APCV) and one patient on continuous positive pressure ventilation (CPAP). As the study progressed, more patients were on pressure control ventilation as this was becoming the preferred mode of NIV in most institutions. The following diagram illustrates the baseline mode of ventilation prior to recruitment (figure 3.2). The table below details the model and duration of ventilation for the 13 patients who completed the randomisation (table 3.2).



**Figure 3.2:** Baseline ventilation mode in participants, n=16

<b>Age</b>	<b>61.5 ± 9.9</b>	<b>years</b>
<b>BMI</b>	<b>27.3 ± 6.8</b>	<b>kg/m<sup>2</sup></b>
<b>Weight</b>	<b>74.3 ± 35</b>	<b>kg</b>
<b>FEV1</b>	<b>0.87 ± 0.36</b>	<b>Litre</b>
FEV1%	37 ± 13	(Predicted)
<b>FVC</b>	<b>1.22 ± 0.47</b>	<b>Litre</b>
FVC%	40 ± 11	(Predicted)
<b>MIP%</b>	<b>60% ± 29</b>	<b>cm H<sub>2</sub>O</b>
<b>MEP%</b>	<b>85% ± 31</b>	<b>cm H<sub>2</sub>O</b>
<b>IPAP</b>	<b>18 ± 4</b>	<b>cm H<sub>2</sub>O</b>
<b>EPAP</b>	<b>7 ± 4</b>	<b>cm H<sub>2</sub>O</b>
<b>RR</b>	<b>18 ± 3</b>	<b>BPM</b>
<b>Male, female</b>	<b>n=8, n=5</b>	
<b>CWD, NMD</b>	<b>n=11, n=2</b>	

**Table 3.1: Patient demographics (Mean ± SD), n=13**

BMI= body mass index, FEV1= forced expiratory volume in first second, VC= vital capacity, MIP%= maximum inspiratory pressure, MEP%= maximum expiratory pressure, IPAP= Inspiratory Positive Airway Pressure, EPAP= Expiratory Positive Airway Pressure, RR= Respiratory Rate, BPM= breaths per minute, CWD= chest wall disease, NMD=neuromuscular disease

<b>Participant No</b>	<b>Model (Mode) of ventilator prior</b>	<b>Years on ventilation</b>
<b>2</b>	<b>Breas 501 (VCV)</b>	<b>11</b>
<b>3</b>	<b>Breas 501 (VCV)</b>	<b>5</b>
<b>4</b>	<b>VPAP 3 ST (PCV)</b>	<b>3</b>
<b>5</b>	<b>Breas 501 (VCV)</b>	<b>11</b>
<b>6</b>	<b>Integra (APCV)</b>	<b>11</b>
<b>7</b>	<b>Resmed (CPAP)</b>	<b>1</b>
<b>8</b>	<b>VPAP 4 (PCV)</b>	<b>0.33</b>
<b>10</b>	<b>VPAP 4 (PCV)</b>	<b>14</b>
<b>11</b>	<b>VPAP 3 STA (PCV)</b>	<b>1.5</b>
<b>12</b>	<b>VPAP 4 ST (PCV)</b>	<b>1</b>
<b>13</b>	<b>VPAP 3 ST (PCV)</b>	<b>2.5</b>
<b>14</b>	<b>VPAP 4 ST (PCV)</b>	<b>1.75</b>
<b>15</b>	<b>VPAP 3 ST (PCV)</b>	<b>9</b>

**Table 3.2 Model (mode) of ventilator and duration of ventilation prior to study in participants who completed randomisation (n=13)**

**VCV= volume control ventilation, PCV= pressure control ventilation,**

**APCV= assist pressure control ventilation, CPAP = continuous positive pressure ventilation,**

**VPAP & integra = ventilator models manufactured by Resmed.**

The participants used their allocated modes as instructed. For the first 10 recruited participants, it was intended to download data from their ventilator for the total six-week period. After the first 10 participants, there were no data downloaded from the ventilators as the software was no longer available. Out of the first 10 participants, data from only seven patients were available. Two of these participants did not complete the

whole study or failed the initial calibration settings and were not randomised. One participant withdrew after completing the second mode and data were not available for download. One of the participants download had the graphs but there was no average daily usage calculated due to a technical error in the software. For the remaining six participants who completed the two modes and had available calculated data, the average usage was  $7.36 \pm 1.1$  (mean  $\pm$  SD) hours.

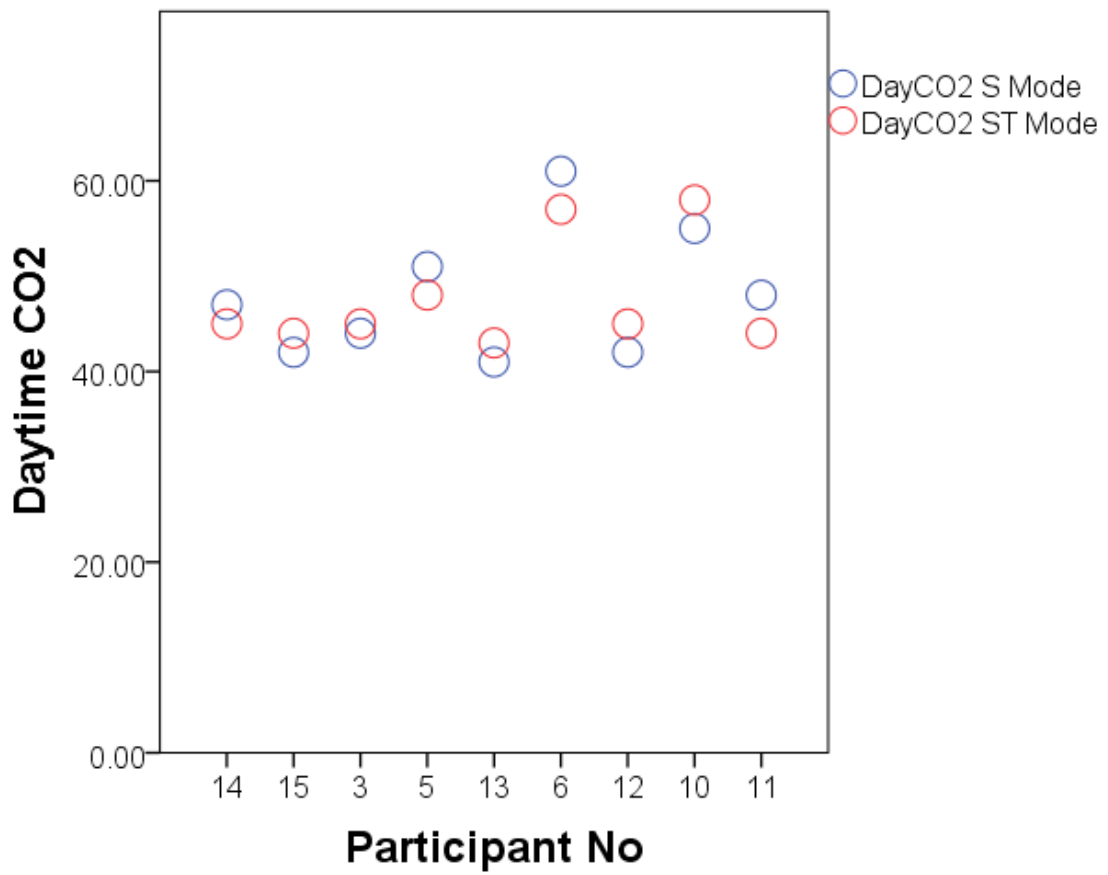
### **3.2 Ventilation parameters**

Ventilation parameters were the primary endpoint in the study between the two modes. These included the difference in: daytime PaCO<sub>2</sub> between the two modes, correction of hypoventilation as calculated by the difference between evening and morning PaCO<sub>2</sub> and degree of oxy-haemoglobin desaturation as described in the methods section.

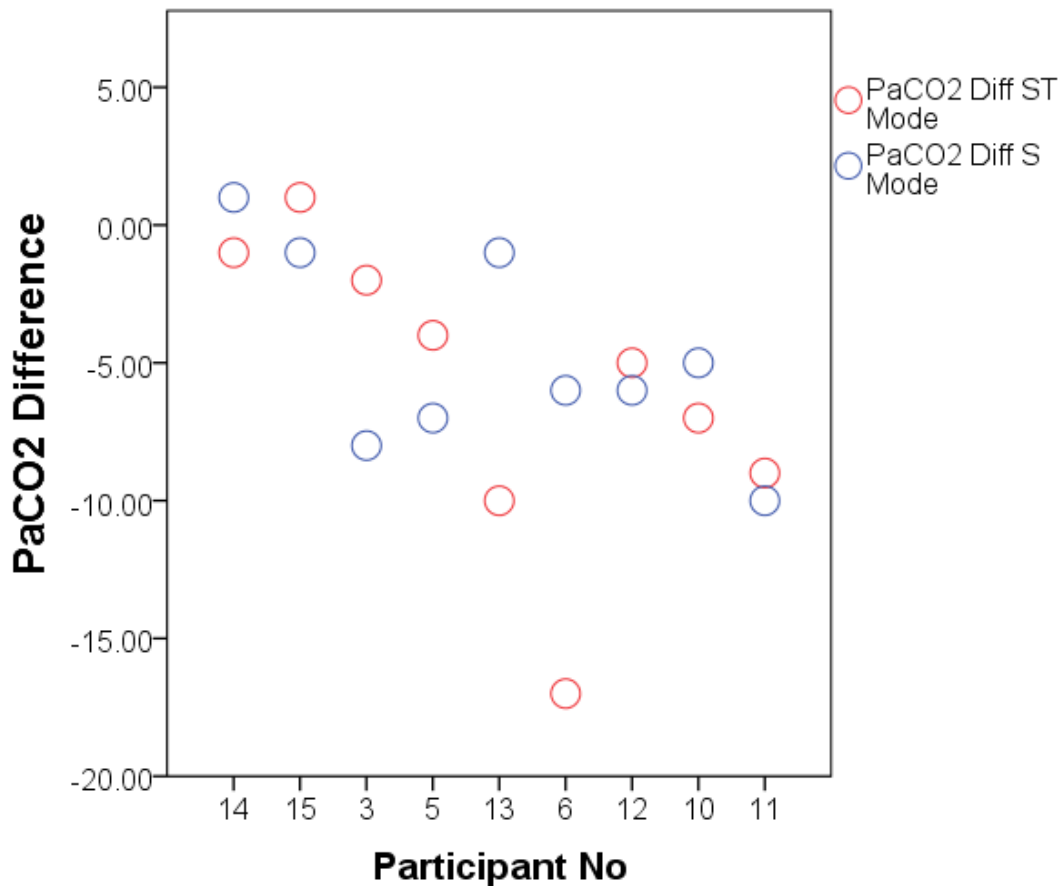
The data for CO<sub>2</sub> measurement were normally distributed and a paired t-test was applied. Only nine pairs of observations were available for comparison as ABGs could not be obtained in some participants at different times. There was no statistically significant difference between the daytime PaCO<sub>2</sub> between the two groups (S Mode  $47.89 \pm 6.75$  mmHg versus the ST mode  $47.67 \pm 5.75$  mmHg, P value 0.829) (Graph 3.1) and (Table 3.3), nor in the PaCO<sub>2</sub> difference between before and after ventilation (S Mode  $-4.78 \pm 3.67$  mmHg versus ST Mode  $-6.00 \pm 5.50$  mmHg, P value 0.528) (Graph 3.2) and (Table 3.3).

CO2	S Mode	ST Mode	t-test	Significance
	Mean (SD)	Mean (SD)	Mean Diff (SD) = S-ST	P value
Daytime PaCO2 (mmHg)	47.89 (6.75)	47.67 (5.75)	0.22 (2.99)	0.829
PaCO2 difference (mmHg)	-4.78 (3.67)	-6.00 (5.50)	1.22 (5.56)	0.528

**Table: 3.3 Paired t-test for PaCO2 difference and daytime PaCO2 (n=9)**



**Graph 3.1: Scatter plot of daytime CO2 (n=9)**



**Graph 3.2 Scatter plot of difference in PaCO<sub>2</sub> (n=9)**

For the time of oxy-haemoglobin desaturation; measured as percentage of total sleep time (TST); the data were not normally distributed; hence a Wilcoxon Signed Rank Test for SpO<sub>2</sub> was applied. In contrast to PaCO<sub>2</sub> measurements, the degree of oxy-haemoglobin desaturation was statistically different between the two groups.

The participants spent more time with oxygen saturation below 90% (SaO<sub>2</sub>\_Time90) on S Mode at 1.4% of TST (0 – 48) versus ST Mode at 0.1% of TST (0 – 2.9), Z -2.22, P value 0.026. There was also more time spent under 85% (SaO<sub>2</sub>\_Time 85) on S Mode at 0.15 % of TST (0 – 8) versus ST Mode at 0.00% of TST (0 - 0), Z -2.37, P value 0.018, (Table 3.4).

The nadir oxygen saturation (SpO<sub>2</sub>) was also statistically different between the groups.

The nadir SpO<sub>2</sub> for the whole study was lower in the S Mode at 82% (52 – 94) versus

the ST mode at 88% (83 – 93), Z -2.22, P value 0.028. The nadir SpO<sub>2</sub> in REM sleep was also lower in the S mode at 85% (52 – 96) versus the ST Mode at 94% (84 – 98), Z -2.29, P value 0.013. Lastly, the nadir SpO<sub>2</sub> was lower in Non-REM sleep in the S Mode at 83% (58 – 94) versus the ST Mode at 88% (83 – 93), Z -2.04, P value 0.041, (Table 3.4).

Oxygen saturation	S Mode	ST Mode		Significance
	Median (Range)	Median (Range)	Z	P value
SpO <sub>2</sub> < 90%	1.4 (0 - 48)	0.1 (0 - 2.9)	-2.22	0.026
SpO <sub>2</sub> < 85%	0.15 (0 - 8)	0 (0 - 0)	-2.37	0.018
Nadir SpO <sub>2</sub> % All study	82 (52 - 94)	88 (83 - 93)	-2.22	0.028
Nadir SpO <sub>2</sub> % REM	85 (52 - 96)	94 (84 - 98)	-2.29	0.013
Nadir SpO <sub>2</sub> % NREM	83 (58 - 94)	88 (83 - 93)	-2.04	0.041

**Table 3.4: Wilcoxon Signed Rank Test for SpO<sub>2</sub> (n=12)**

SpO<sub>2</sub>= Oxygen saturation by pulse oximetry, REM= Rapid Eye Movement sleep, NREM= Non-Rapid Eye Movement sleep

Two participants described side effects from either mode of ventilation. One participant (number 9) felt uncomfortable from the mask and did not like the allocated first mode. Of note, the participant was on volume cycled ventilation (VCV) prior to randomisation. The participant pulled out after the first mode.

The other participant (number 15) reported feeling uncomfortable with difficulty in triggering, delay in ventilation as well as struggling to consolidate sleep on mode 2. The participant continued with the full randomisation and completed all the sleep studies. The patient was on pressure control ventilation (PCV) before randomisation.

### **3.3 Respiratory events**

The results of indices for respiratory events are divided into Obstructive Apnoea Index (OAI), Mixed Apnoea Index (MAI), Central Apnoea Index (CAI), and Apnoea Hypopnoea Index (AHI) all reported per hour (hr).

A non-parametric test “Wilcoxon Signed Ranks Test” was utilised as the data failed the test of normality and were skewed. A number of statistically significant values were found in favour of Spontaneous Timed Mode.

There were fewer respiratory events in ST mode than in S mode in many parameters including the Obstructive Apnoea Index in all sleep (median 0.00, range 0-0) and (median 2, range 0-64) respectively,  $Z -2.666$ ,  $P 0.02$ .

Mixed Apnoeas were also reduced in the ST mode in comparison to the S mode in total sleep (median 0.00, range 0-0) and (median 1, range 0-12) respectively,  $Z -2.366$   $P 0.018$ .

Central Apnoeas were lower in the ST mode than S mode similar to other types of apnoeas in total sleep (median 0.00, range 0-1) and (median 4, range 0-58) respectively,  $Z -2.803$ ,  $P 0.008$ .

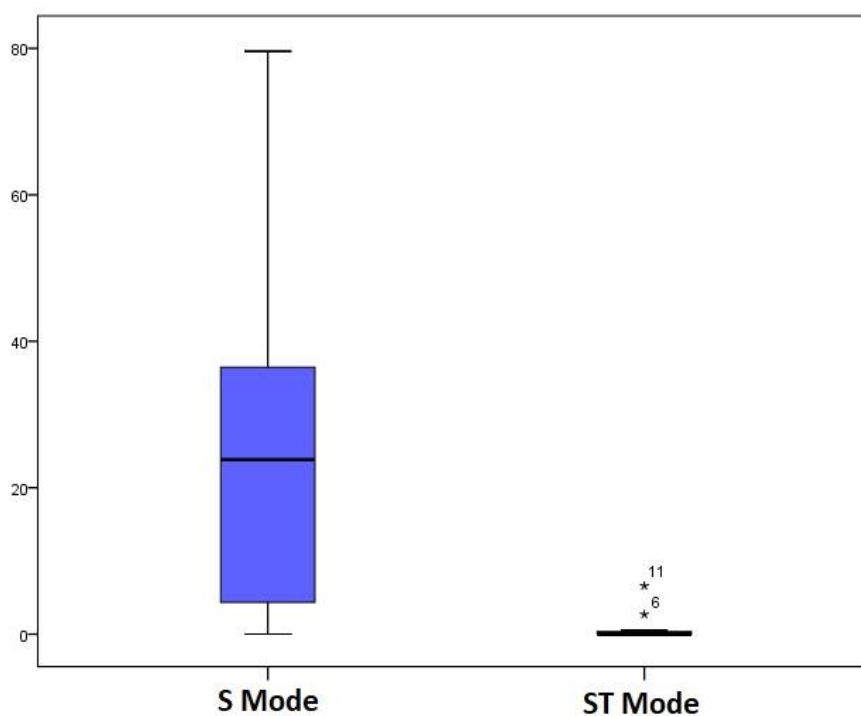
Finally, the overall Apnoea Hypopnoea Index for the whole study; a common measure for characterisation of sleep disordered breathing; was lower in the ST than the S mode (median 0.00, range 0-7), and (median 24, range 0-80) respectively,  $Z -2.756$ ,  $P 0.006$ , (Graph 3.3), (Table 3.5).

Respiratory events/hr	S Mode	ST Mode	WSRT	Significance
	Median (range)	Median (range)	Z value	P value
OAI	2 (0-64)	0 (0-0)	-2.666	.008
MAI	1 (0-12)	0 (0-0)	-2.366	.018
CAI	4 (0-58)	0 (0-1)	-2.803	.005
AHI	24 (0-80)	0 (0-7)	-2.756	.006

**Table 3.5: Wilcoxon Signed Ranks Test for Respiratory Events (n=12)**

OAI= Obstructive Apnoea Index, MAI= Mixed Apnoea Index, CAI= Central Apnoea Index,

AHI= Apnoea Hypopnoea Index, hr= hour



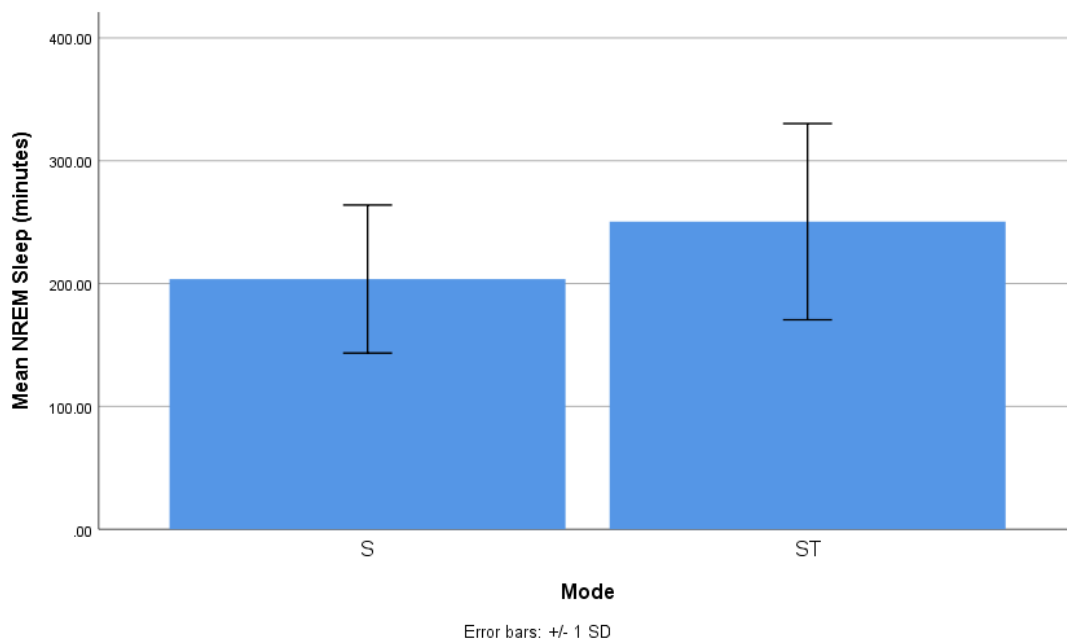
**Graph 3.3: Box plot of Total Apnoea Hypopnoea Index in total sleep (P= 0.006)**

### 3.4 Sleep Parameters

A paired t-test was performed as the data were normally distributed except for total sleep time and the number of awakenings when a non-parametric test was used.

Sleep efficiency between the two modes was not statistically different although there was a trend towards better efficiency with spontaneous timed mode in comparison with spontaneous mode (Mean  $64.09 \pm 17.859$  and  $55.27 \pm 18.511$  respectively, P 0.089).

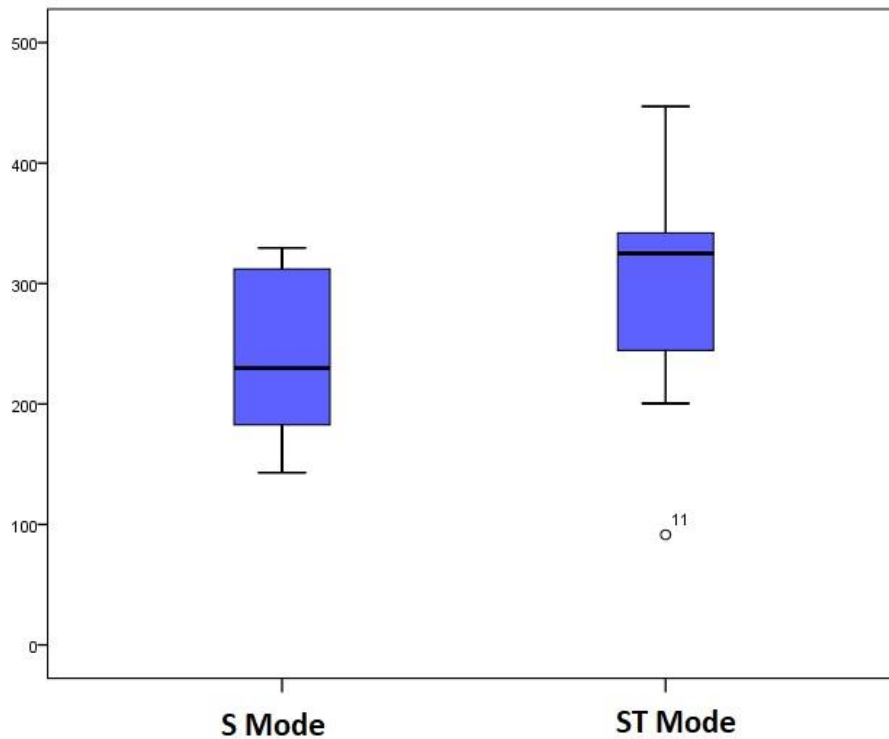
Total NREM sleep was significantly greater in spontaneous timed mode than in spontaneous mode (Mean  $250.15 \pm 79.943$  minutes and  $203.42 \pm 60.111$  minutes respectively, P 0.01), (Graph 3.4). Total REM sleep was not statistically different between the ST mode and S mode (Mean  $42.19 \pm 19.367$  minutes and  $35.58 \pm 15.944$  minutes, P 0.349). The results of the paired t-test are displayed below (Table 3.6 -A)



**Graph 3.4: Total NREN mean and standard deviation (SD), n=12, P = 0.01**

For total sleep time and the number of awakenings, a non-parametric test was applied “Wilcoxon Signed Ranks Test” as the data were not normally distributed. The results are displayed as mean and range.

Total sleep time was greater in spontaneous timed mode than spontaneous mode with a median of 321 (92-447) minutes and 230 (143-330) minutes respectively,  $Z = -2.197$ , ( $P = 0.028$ ) (graph 3.5). On the other hand, the number of awakenings per hour during sleep was not different between the two modes with a median value of 23 (10-55) for the ST mode and 25 (9-60) for the S mode,  $Z = -.204$ , ( $P = 0.838$ ), (Table 3.6 -B)



**Graph 3.5: Total sleep time Boxplot, n= 12, P= 0.028**

Sleep parameter	S Mode	ST Mode	t-test	Significance
	Mean (SD)	Mean (SD)	Mean Diff (SD) = S-ST	P value
Sleep Efficiency %	55.27 (18.51)	64.99 (18.34)	-9.73 (18.07)	0.089
NREM Total (min)	203.42 (60.11)	257.71 (78.50)	-54.29 (60.86)	<b>0.01</b>
REM Total (min)	35.58 (15.94)	43.13 (19.92)	-7.54 (26.71)	0.349

**Table 3.6 -A: t-test for Sleep parameters (normally distributed data) (n=12)**  
NREM= Non-Rapid Eye Movement, REM= Rapid Eye Movement, min = minutes

Sleep parameter	S Mode	ST Mode	WSRT	Significance
	Median (range)	Median (range)	Z value	P value
Total sleep time (min)	230 (143-330)	321 (92-447)	-2.197	.028
Awakenings / hr	25 (9-60)	23 (10-55)	-.204	.838

**Table 3.6 -B: Wilcoxon Signed Ranks Test (WSRT) for Total Sleep Time (TST) in minutes and total number of awakenings/hour (n=12)**

min=minute, hr=hour

### 3.5 Discussion

The results of study 1 indicated that spontaneous timed mode generally provided better nocturnal oxygenation than spontaneous mode, although there was no statistically significant difference between the two modes in measures of change in CO<sub>2</sub> after overnight ventilation or in daytime CO<sub>2</sub>.

The primary outcome of this study was assessment of ventilatory parameters between the two modes of ventilation, reflected in delta CO<sub>2</sub>, daytime CO<sub>2</sub>, and oxygenation, which is the principal physiological goal of treatment with non-invasive ventilation. If ventilation is successful, this is usually reflected in improvement or normalisation of daytime carbon dioxide measurements; as well as a decrease in the difference between evening and morning carbon dioxide levels. These two parameters are important measures of successful ventilation.

The presence and severity of nocturnal oxy-haemoglobin desaturation is also an important measure of successful ventilation. This was assessed as Oxygen saturation levels below 90% and 85% as a percentage of total sleep time, as well as by nadir oxy-haemoglobin desaturation in each phase of sleep and in total sleep. The lower the values, the less effective the mode of ventilation is.

In this study, when we compared correction of carbon dioxide (CO<sub>2</sub>) levels before and after ventilation, and the absolute value of daytime CO<sub>2</sub>, there was no statistically significant difference between the two modes with a tendency towards mild improvement on spontaneous timed mode. This may be due to the study being underpowered to detect such difference. Also, the participants in this study were clinically stable patients, already established on non-invasive ventilation, hence it is possible that significant changes in CO<sub>2</sub> would have been more difficult to see than if they were de novo patients. The study was also run over a six-week cycle with a two-week washout period. Previous studies have indicated that changes in ventilation parameters can take up to three months to be seen [88].

On the other hand, we found that Spontaneous Timed mode was more effective in maintaining stable nocturnal oxygenation. This was illustrated in the percentage of time with low oxy-haemoglobin level below 90% and 85% in the whole overnight study. It was also evident in the nadir oxy-haemoglobin level in both REM and NREM sleep as well as for the total sleep study on each mode of ventilation overnight.

Previous work by an English group led by Restrict et al., assessed whether nasal pressure support ventilation in spontaneous mode, was equivalent to nasal intermittent positive pressure ventilation, which was delivered in spontaneous timed mode with a backup respiratory rate. The participants also spent a night without ventilation, which acted as control. The patients were heterogeneous. Five patients had chronic obstructive respiratory disease (COPD) and the remaining seven patients had extrathoracic restrictive lung disease, with either neuromuscular disease or chest wall disease. The patients with extrathoracic lung restriction had severe reduction in their vital capacity to about 30% predicted. The average arterial partial pressure of carbon dioxide in blood was 52 mmHg. The patients received the same inspiratory positive airway pressure

(IPAP) and expiratory positive airway pressure (EPAP) in each of the night they were ventilated. The backup rate for the spontaneous timed mode was not stated in the manuscript. The patients were monitored mainly for respiratory parameters but polysomnography was not performed. The results were similar to this research in the fact that there was no difference between spontaneous mode and spontaneous timed mode in carbon dioxide levels in the blood, while both modes did show an improvement when compared to the control night on no ventilation. On the other hand, the study was different from this research with regards to the degree of drop in nocturnal oxygen levels, where again their results showed improvement from the control night on both modes but there was no significant difference between the two modes themselves. This may be partly explained by the fact that this English study included patients with chronic obstructive airways disease (COPD) where parenchymal lung disease could have played a role in hypoxaemia levels. It is also unclear whether the participants had adequate backup rate or not as this was not stated in the study methods [201].

In addition to the improvement in overnight oxygenation, our research study assessed the difference in sleep parameters between spontaneous timed mode and spontaneous mode. The results showed that respiratory events were fewer with spontaneous timed mode than in spontaneous mode with a statistically significant difference in the total apnoea hypopnoea index and all other indices including obstructive events, central events and mixed apnoea events.

Drawing from the obstructive sleep apnoea literature, there is good correlation between the number of respiratory events (AHI) and hypertension, heart failure, stroke and coronary artery disease as demonstrated in the large Sleep Heart Health Study [207, 208] but also in smaller studies [209, 210]. Whilst it is acknowledged that this a different group of patients, they share physiological disturbances overnight that are

similar to the cohort of patients in this study. In fact, in the study by Georges et al., in patients with amyotrophic lateral sclerosis, the presence of upper airway obstruction was associated with shorter survival [49]. Although this is also a different group of neuromuscular disease patients, where the condition is usually more rapidly progressive than the cohort in this research study, it still highlights the need for optimisation of ventilation and effective treatment of upper airway obstruction.

Finally, in this research study, sleep quality overall appeared better in spontaneous timed mode than spontaneous mode. There was a statistically significant greater sleep time during Non-Rapid Eye Movement sleep as well as a significantly greater overall total sleep time in ST than in S mode, and a trend towards a longer sleep time in Rapid Eye Movement sleep; however, the difference was not statistically significant. This may be related to the fact that the total duration of REM sleep is generally shorter than Non-REM; hence a larger number of participants is required to see a true difference.

When we compare our results to previous studies in patients with neuromuscular disease investigating sleep parameters under different ventilation settings, optimal ventilation settings were associated with better sleep quality. In the study by Fanfulla et al., who evaluated daytime clinically adjusted ventilation to physiologically adjusted ventilation, tailored to the patient's respiratory effort, there was better sleep efficiency and a trend towards better total sleep time in the physiologically adjusted ventilator settings group than clinically adjusted group [135]. In the recent study by Hannan et al., the use of polysomnographic titration of non-invasive ventilation to reduce patient-ventilator asynchrony (PVA) was associated with better sleep quality and less somnolence [180]. From a functional point of view, moderate sleep restriction has been associated with dose-dependent deficits in neuro-behavioural function as demonstrated by Van Dongen et al. in their study on 48 healthy subjects [134]. The study

demonstrated that there is a cumulative effect of chronic lack of good quality sleep on neuro-behavioural performance when continued over a period of 14 nights. In this research study, we found a decrease in median total sleep time by 91 minutes, mostly during non-REM sleep, in S mode when compared with ST mode. This could potentially have a cumulative effect on neuro-behavioural function if it happens on a long-term basis.

The reduction in respiratory events, the improvement in oxygenation parameters and better sleep efficiency are all important goals of mechanical ventilation. These results confirm previous work done by other authors who studied the effect of different types of non-invasive ventilation on respiratory and sleep parameters. More importantly, the results of this research may have long term benefits for this group of patients, as established by the following studies who assessed long term effects of NIV.

In the study by Barbe' et al., that assessed long term effects of nasal intermittent positive pressure ventilation (NIPPV) in eight stable patients with neuromuscular disease, similar results were seen. The patients had already been receiving NIPPV for at least one year. The authors assessed the effect of controlled volume-cycled ventilation, without the use of positive end expiratory pressure (PEEP), on daytime arterial blood gas levels, respiratory muscle function, lung mechanics and sleep-related parameters. Baseline questionnaires were conducted to assess the participants' symptoms, such as somnolence, insomnia, nightmares, morning headaches and/or snoring, with somnolence being the commonest symptom. After initiation of ventilation, baseline values were obtained for the respiratory and sleep parameters described above by using a spirometer attached to the expiratory circuit and undergoing a sleep study. The participants underwent a second sleep study about  $10 \pm 2$  months later. Assessment of the lung function was done at the longest available period of follow up after initiation

on NIPPV ( $18 \pm 2$  months). The results showed improvement in daytime oxygenation, reduction in arterial carbon dioxide levels, apnoea hypopnoea indices, nocturnal oxygenation parameters, sleep architecture as well as sleep efficiency. There was no significant change in lung mechanics [156].

These results are similar to another study by Annane et al. who assessed the effect of long-term ventilation in a cohort of 16 patients with extra-thoracic lung disease; including neuromuscular disease and chest wall disease; studied at six months, one and three years. Although this study was different from this research, in that it involved volume-cycled ventilation rather than pressure cycled ventilation, it did highlight that effective ventilation is associated with long term improvement in oxygenation, sleep efficiency and a reduction in the Apnoea Hypopnoea Index [157].

Although these studies are not randomised controlled studies, they illustrate that these parameters are a measure of successful ventilation with improved outcomes for patients with neuromuscular and chest wall disease.

In patients with obstructive sleep apnoea; a somewhat less severe form of sleep disordered breathing; all of these parameters including high apnoea hypopnoea index and severe fall in nocturnal oxygen saturation have been implicated in poor quality of life and increased cardiovascular risk; including ischaemic heart disease, cerebrovascular accidents and arrhythmias [211, 212]. Treatment with CPAP therapy has been previously shown to protect against cardiovascular complications in patients with obstructive sleep apnoea syndrome [213, 214]; although a recent multicentre study showed no benefit in secondary prevention of cardiovascular disease [215]. Whilst there are no data to suggest similar cardiovascular complications in our cohort of patients, the symptoms of poor sleep efficiency, poor oxygenation and respiratory events overnight are very similar, suggestive of similar potential risks long term.

Effective nocturnal ventilation may possibly have protective effects against cardiovascular complications; however, further larger long-term studies are required to establish any significant benefit.

Our study was limited to stable patients with extrathoracic restrictive lung disease including chest wall and neuromuscular disease. The results may be different in the acute setting or in other patient groups such as patients with motor neurone disease patients whose disease tends to progress faster than does that in our cohort of patients. The study was also a short term one over a six-week period. Longer term studies may identify other significant differences between the two modes, such as day time respiratory failure when measured by PaCO<sub>2</sub> levels.

In conclusion, ST mode ventilation did not further improve daytime hypoventilation in comparison to S mode ventilation; as measured by carbon dioxide levels. However, it did result in improved nocturnal oxygenation, sleep quality and fewer respiratory events, in stable patients with chest wall and neuromuscular disease. This may provide better long-term cognitive outcomes and reduce the risk of cardiac complications or mortality; however, we did not assess this in the current study. A longer term study is required to assess long term benefits such as reduction in morbidity and mortality with implementation of optimal modes of ventilation.

## **Chapter 4**

### **4 Impact of ventilation mode on sleepiness and vigilance and patient preference**

The aim of these evaluations was to assess the impact of the two different modes of ventilation on the participants with regards to sleepiness, psychomotor vigilance testing and their preference of which mode they felt was better in a number of parameters. The sleepiness evaluation was done through a standardised and well-validated questionnaire the “Epworth sleepiness scale” (ESS) (appendix 1). The psychomotor vigilance was tested using the psychomotor vigilance test (PVT) equipment as described above in the methods section. The preference questionnaire involved assessment of their breathing comfort as compared to their usual ventilator, their level of energy during day time as compared to their usual daytime activity, their grading of how refreshed they felt in the morning as compared to usual, their experience of any morning headaches as compared their usual circumstances and finally rating of their quality of sleep as compared to their usual night sleep. The participants were also asked to compare the two modes together and indicate their preference in regards to the above five parameters. (appendix 2).

Below are the individual results of each of these assessments.

#### **4.1 Epworth sleepiness scale (ESS)**

A total of 14 out of 16 participants who were randomised, completed the Epworth Sleepiness Scale questionnaire; however, only 13 participants completed the randomisation and filled out the ESS questionnaires at baseline and after each mode. The participants had a mean baseline ESS of  $5 \pm 4$  on their own mode of ventilation before randomisation.

The study showed a positive impact of the ventilation mode on the Epworth sleepiness scale, a well-validated measure of sleepiness. The participants were sleepier after two weeks on Spontaneous mode (S) (mean score  $7 \pm 5$ ) than Spontaneous Timed mode (ST) (mean score  $4 \pm 4$ ), which was statistically significant, P 0.032 (table 4.1).

When compared to baseline Epworth sleepiness scale (ESS), the mean change for S mode was an increase by  $0.54 \pm 5.2$ , when compared to ST mode which resulted in a decrease in ESS by  $-1.3 \pm 3.5$ , that was also statistically significant, P 0.045 (table 4.2).

Three participants on S mode had an ESS score of more than 10; however only one of these participants had a high baseline ESS above 10. In the ST mode only one participant had a high ESS above 12; however, this was also their baseline ESS prior to randomisation.

Parameter	Baseline	S Mode	ST Mode	t-test	Significance
	Mean (SD)	Mean (SD)	Mean (SD)	Mean Diff (SD) = S-ST	P value
ESS	5 (4)	7 (5)	4 (4)	2.23 (3.32)	0.032

**Table 4.1 Paired t-test for Epworth Sleepiness Scale (n=13)**

Parameter	S Mode	ST mode	t-test	Significance
	Mean (SD)	Mean (SD)	Mean Diff (SD) =S - ST	P value
ESS change from baseline	0.54 (5.2)	- 1.3 (3.5)	1.85 (2.97)	0.045

**Table 4.2 Paired t-test for change in ESS from baseline (n=13)**

SD=standard deviation, ESS= Epworth sleepiness scale, S= spontaneous mode, ST= spontaneous timed mode

## 4.2 Results for Psychomotor Vigilance Test (PVT)

A total of 12 participants completed the two psychomotor vigilance tests. One patient out of the 13 participants only completed one test.

The two main values that were assessed, were the mean value of the PVT performance and the number of lapses of > 500 msec as defined in the relevant methods section.

A paired t-test was performed to compare the means of the psychomotor vigilance test performed after 2 weeks on each mode, and for the mean difference from baseline PVT results, as data appeared normally distributed. The results are reported in milliseconds (msec).

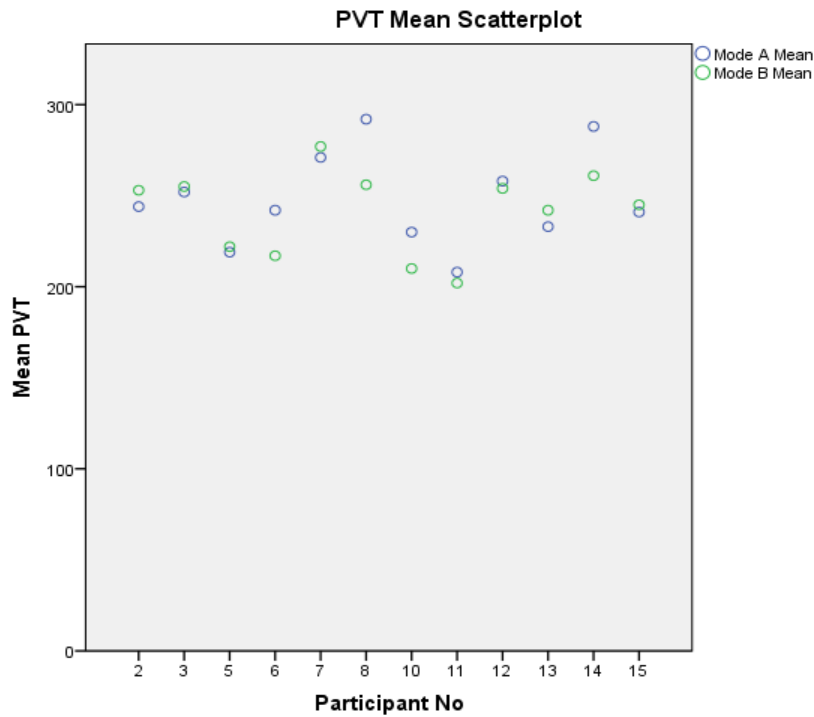
The baseline mean PVT value before randomisation, while the participants were still on their own mode of ventilation, was  $268 \pm 53$  msec. The mean value for the S Mode was  $248 \pm 26$  msec versus  $241 \pm 23$  msec for the ST Mode as per the scatterplot below (graph 4.1). There was no significant difference between the two groups with a mean difference of  $7 \pm 16$  (P 0.153) (Table 4.3). For the difference in means from baseline, the spontaneous mode had a mean difference of  $-1 \pm 33$  msec and the spontaneous timed mode had a mean difference from baseline of  $-16 \pm 25$  msec. Similarly, there was no

significant difference between the change from baseline between the two groups with a mean difference of  $15 \pm 29$  msec (P 0.095), (table 4.3).

A Wilcoxon signed rank test (WSRT) was used to compare the number of lapses between spontaneous mode and spontaneous timed mode and also for the difference in lapses from baseline as the data was not normally distributed. The results are presented as median and range.

The baseline for median lapses of  $> 500$  msec before randomisation, while the participants were still on their own mode of ventilation was 4 (0-28). The median value for S mode was 2 (0-6) and the median value for ST mode was 1 (0-13). There was no significant difference in the ranking between the two modes,  $Z = -1.134$ ,  $P = 0.257$  (table 4.4).

For the difference in lapses from baseline, the median change for S mode was -1.5 (-13 - +4) and for the ST mode was -2 (-15 - +1). There was no statistically significant difference between for the change from baseline for the two modes,  $Z = -1.136$ ,  $P = 0.256$  (table 4.4).



**Graph 4.1: Scatter plot of PVT means for S and ST modes, n=12**  
 S= spontaneous mode, ST= spontaneous timed mode

Parameter	Baseline	S Mode	ST Mode	t-test (S-ST)	Significance
	Mean (SD)	Mean (SD)	Mean (SD)	Mean Diff (SD)	P value
PVT (msec)	268 (53)	248 (26)	241 (23)	7 (16)	0.153
PVT Diff		-1 (33)	-16 (25)	15 (29)	0.095

**Table 4.3: Paired t-test for means of PVT performance and mean difference from baseline (n=12),**

PVT= psychomotor vigilance test, SD= standard deviation, Diff= difference,  
 PVT Diff= difference in mean value from baseline, msec= milliseconds

Parameter	Baseline	S Mode	ST Mode	WSRT	Significance
	Median (R)	Median (R)	Median (R)	Z value	P value
<b>Lapses (No)</b>	4 (0-28)	2 (0-6)	1 (0-13)	-1.134	0.257
<b>Lapses Diff</b>		-1.5 (-13 - +4)	-2 (-15 - +1)	-1.136	0.256

**Table 4.4 Wilcoxon signed rank test (WSRT) for number of lapses in PVT test and difference from baseline (n=12)**

S= spontaneous mode, ST= spontaneous timed mode, R=range, No= number, Diff= difference

### 4.3 Patient symptoms and preference

A total of 13 participants completed the questionnaires for their symptoms on each mode of ventilation in comparison to their own mode of ventilation. The questionnaire involved questions with regards to breathing comfort, energy levels, feeling fresh in the morning, development of headaches, and the overall sleep quality. The answers were divided into five categories and graded as described in the relevant methods section and appendix (2).

Ordinal regression analysis was used to test each separate symptom response and also for an aggregate score of all the responses. The results are displayed below.

For each symptom response as well as the aggregate score, the S mode was associated with decreased lower cumulative scores compared to the ST mode; however, there was no statistically significant difference between the two modes as displayed below (table 4.5).

The results of the second questionnaire involved the direct comparison between the two modes to reflect patient preference (appendix 2), which showed a similar pattern to the

S mode being associated with lower cumulative scores than the ST mode; however, none of the results were statistically significant as displayed below (table 4.6).

	Breathing comfort	Energy levels	Fresh	Headaches	Sleep quality	Aggregate Score
Estimate (S displayed) as C/W own vent	-0.573	-1.04	-1.23	-1.28	-0.46	-0.891
P value	0.446	0.177	0.102	0.298	0.528	0.207

**Table 4.5 Ordinal regression for symptoms compared with own ventilator (n=13)**

S= spontaneous mode displayed (in reference to spontaneous timed (ST) mode),

C/W= compared with, vent=ventilator

	Breathing comfort	Energy levels	Freshness	Headaches	Sleep quality
Estimate (S displayed) as C/W (ST)	-0.706	-0.548	-0.409	-0.746	-0.956
P value	0.348	0.452	0.576	0.315	0.2

**Table 4.6 Ordinal regression for direct comparison between S and ST mode (n=13)**

S= spontaneous mode displayed (as compared with ST mode), ST=spontaneous timed mode,

C/W= compared with

#### **4.4 Discussion:**

The impact of ventilation mode on patient symptom and function is very important. We undertook an assessment of the impact on excessive daytime sleepiness, and psychomotor performance after each mode of ventilation and found reduced subjective sleepiness in the Spontaneous timed group. There was a significant improvement in the Epworth sleepiness scale in spontaneous timed mode when compared with spontaneous mode, however, there was no significant difference in patient symptoms, preference or psychomotor performance between the two modes.

Firstly, the Epworth Sleepiness Scale which is a commonly used and well-validated tool for assessing subjective sleepiness was assessed at baseline and after each mode of ventilation. The results showed that participants were less sleepy on the Spontaneous Timed Mode than Spontaneous mode with a mean difference in ESS score of  $2 \pm 3$ . There was also an improvement in the ESS score from baseline in spontaneous timed (ST) mode only by  $1.3 \pm 3.5$  but not in spontaneous mode. Previous work indicates that treatment with non-invasive ventilation is associated with improvement in the degree of daytime sleepiness. In the study by Guilleminault et al., who assessed the impact of bilevel non-invasive ventilation on sleep disordered breathing in twenty patients with neuromuscular disease, a significant improvement was seen. The participants were symptomatic with daytime sleepiness and fatigue. After treatment with non-invasive ventilation, the participants were assessed in the short term after four weeks as well as long term after one year by filling out an Epworth sleepiness scale (ESS) score, but the authors also confirmed their findings by doing multiple sleep latency tests (MSLT) The results showed that the mean Epworth sleepiness scale (ESS) score dropped down both at the short and long term from baseline. Although there was some discrepancy with

the MSLT in some patients, the results of the multiple sleep latency test also showed an improvement in sleepiness with an increase in sleep latency [216].

In a large multicentre study by Masa et al., 86 patients with obesity hypoventilation but without associated severe sleep apnoea, were randomised to either conservative management with lifestyle measures versus non-invasive ventilation. The authors used pressure-cycled ventilation with assured volume as the mode of ventilation. Apart from improvement in gas exchange, the study also showed improvements in sleepiness as assessed by the Epworth sleepiness scale as well as health-related quality of life questionnaires. The Epworth sleepiness scale scores improved significantly with non-invasive ventilation by 1.7 points in comparison with lifestyle measures. The health-related quality of life assessments, particularly from the mental health aspects, also improved significantly [217].

Given that the Epworth sleepiness scale has been widely validated in the sleep apnoea literature and applied consequently to patients with sleep disordered breathing from other causes, such as extrathoracic lung disease, adapting some of the literature from the sleep apnoea population is acceptable, particularly given that there haven't been many studies in the latter group of patients. One study by Patel et al. assessed the effect of continuous positive airway pressure (CPAP) therapy in patients with obstructive sleep apnoea (OSA). The aim of the study was to determine the minimum clinically important difference in the Epworth sleepiness scale score that affects the feeling of being less sleepy. The results of the study showed that a difference of -2 to -3 was clinically significant for patients [218].

In this research study, a significant improvement in the Epworth sleepiness scale score was achieved between spontaneous timed mode and spontaneous mode of at least two points. There was also an improvement in change from baseline in some patients of

more than 2 points. Some of the participants who remained sleepy after treatment allocation, usually had a highly pathological ESS score at baseline, except for one participant who scored much higher on spontaneous mode when compared to baseline (increase from 4 to 13) but increased mildly to 6 on spontaneous timed mode. Clinically, the results of the study indicate that these patients are more likely to remain awake during the daytime on Spontaneous Timed mode; and hence likely to have improved quality of life.

The psychomotor vigilance test is a validated measure of assessing the degree of alertness and ability to perform tasks. Previous studies suggested that controlled sleep deprivation between four and six hours of total sleep as compared with eight hours in 48 normal subjects over 14 days affected psychomotor skills, as assessed by PVT [134]. We performed this test on each participant prior to starting on each mode of ventilation and after 2 weeks on the two different modes. Although the participants did slightly better on Spontaneous Timed mode, there was no significant difference in the mean value obtained on each mode; hence it can be concluded that despite a statistically significant difference in sleep quality, Epworth Sleepiness Scale, the number of ineffective efforts and respiratory and ventilation parameters this was not enough to affect patient performance in the psychomotor vigilance test to a significant extent. Previous studies in obstructive sleep apnoea patients evaluated the use of the psychomotor vigilance test performance after continuous positive airway pressure (CPAP) treatment. In the study by Deering et al., 114 patients with OSA underwent baseline PVT before starting on CPAP therapy for six months then re-evaluated. CPAP adherence was monitored. There was no significant difference in the mean reaction time or the mean number of lapses before or after therapy except for a subgroup of patients with higher lapses at baseline and in those who had higher adherence to CPAP therapy

[219]. A similar result was found in the study by Hsien Li et al. who evaluated the effect of three months of CPAP therapy on sleepiness and cognitive tasks including undergoing psychomotor vigilance testing and filling out the Pittsburgh Sleep Quality Index (PSQI) and the Epworth sleepiness. Whilst there was an improvement in daytime sleepiness and increased executive function, there was no significant effect on psychomotor vigilance tests [220].

In a study by Piper et al. [86], the authors compared CPAP therapy to bilevel ventilatory support in patients with obesity hypoventilation syndrome for a number of outcomes including ventilatory failure, subjective sleep quality, daytime sleepiness, adherence and psychomotor vigilance testing. Whilst there was no significant difference in the primary outcome of change in daytime CO<sub>2</sub> levels, nor in the secondary outcomes of subjective sleepiness, health-related quality of life questionnaire and adherence to therapy, there was a significant improvement in subjective sleep quality and the slowest 10% of reaction times in the PVT test.

Our current research study is underpowered to detect a significant difference in PVT performance and a larger number of participants may be required to achieve significant results.

An assessment of the participants' symptoms and indication of their preference after each mode of ventilation was also undertaken. The participants were asked how they felt on each mode of ventilation in comparison to their normal ventilation and also whether there was a difference between the two modes tested in this study as described in the relevant methods section and appendix 2. The questionnaires were conducted after two weeks on each mode to give them enough time to adapt to the new mode.

A lot of the participants were already on spontaneous timed mode except for 3 participants, one previously on volume-cycled ventilation, one on continuous positive

pressure ventilation and one on assist pressure control ventilation (APCV). The results indicated that the participants rated the spontaneous mode less than spontaneous timed mode; however, the results were not significant. When comparing the two modes of ventilation together, again they rated the ST mode better than S mode, but the results were also not significant. It is quite possible that some of the participants realised which mode of ventilation they were on, despite strict blinding techniques. It is quite possible that this may have biased some of the answers in the questionnaires and affected the results. The same applies to the questionnaire for the Epworth sleepiness scale scores and bias due to recognition of the ventilation mode cannot be excluded. Overall, there was no significant difference between the two modes when compared to their normal mode of ventilation or when compared directly with regards to patient preference although there was a trend towards better scoring for symptoms or preference in the spontaneous timed mode than the spontaneous mode.

In conclusion, the participants appeared to be less sleepy on ST mode than S mode; however, neither mode was associated with pathological sleepiness. This change in subjective sleepiness did not translate to a difference in cognitive function, as measured by psychomotor performance, although the study was underpowered for identifying smaller differences in this outcome. There was no difference in symptom rating or preference between the two modes by the participants.

## **Chapter 5: Study 2 “Measurement of intra-oesophageal pressure (Poes) as a marker of respiratory effort during non-invasive ventilation in patients with extra-thoracic restrictive lung disease”**

### **5.1 Introduction**

Triggering of the ventilator is defined as “a patient’s spontaneous effort at initiating a breath followed by a mechanical response from the ventilator” [10]. Triggering of the ventilator by the patient is a complex operation that is affected by a number of variables. It is an interactive process between the patient and ventilator determined, not only by the ventilator settings but also by patient characteristics, including their physiological reserve and underlying medical condition.

Failure to trigger the ventilator can be due to a number of causes including, for example, respiratory muscle weakness, poor compliance of the respiratory system, the presence of high intrinsic positive end-expiratory pressure (intrinsic PEEP) or the presence of leak. It is an important cause of dys-synchrony between the patient-initiated breath and the ventilator delivered breath; defined as mismatch between the patient and ventilator inspiration and expiration [188] or in other words uncoupling of the patient’s respiratory efforts and the ventilator pressure support. A period of ten seconds and three consecutive breaths have been described as a minimum [169]. Patient-ventilator dys-synchrony may cause patient discomfort, sleep disruption and sub-optimal ventilatory support.

To determine any differences in interaction between the patient and ventilator in the two ventilation modes; a sub-study was performed in a subset of patients. The original study design was maintained except that in this subset of patients an oesophageal

balloon was inserted by the principal investigator to indirectly measure pleural pressure; a surrogate for patient effort. By measuring oesophageal pressure integrated with other parameters in the sleep study ineffective (or wasted) efforts by the patient could be assessed. This was defined as “failure of the patient’s inspiratory effort to trigger the ventilator”, a possible cause of dys-synchrony, discomfort and poor quality sleep [188]. Improving synchrony can lead to better adherence to therapy, as illustrated in a recent Australian study by Hannan et al. [180].

**The aim of the study was to compare the two modes for the presence of ineffective (wasted) efforts by the participants, that fail to trigger the ventilator, through the insertion of an oesophageal balloon. In addition, poor triggering was assessed as the time in seconds when there appeared to be effort made by the patient that was not rewarded by a mechanical breath.**

Prior to the study, external calibration of the balloon-catheter system had to be performed to ensure that the system is reliable and able to work under physiological conditions. This is described in detail in the following section.

## **5.2 Calibration of Equipment for oesophageal balloon system**

### **5.2.1 Background**

The measurement of oesophageal pressure remains mostly limited to research studies due to patient or participant inconvenience as well as the time required to assemble the system. Although balloon-catheter systems are commercially available now, they were not readily available at the start of the study and therefore a bespoke system was manually assembled; as described below; according to known literature. The balloon and the catheter were purchased separately.

Before starting to use this manually assembled system, the technique had to be developed and then tested, to ensure these measurements and results were accurate. The aim was to make sure that the system could work under different physiological settings in the participants [141, 221].

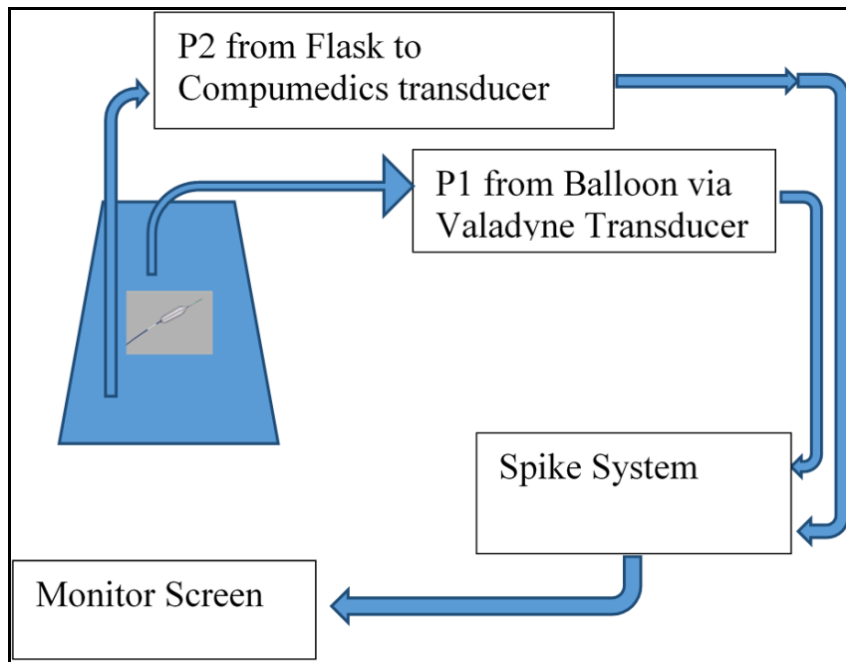
The initial external calibration was achieved by testing the frequency response of the balloon catheter system as described below.

### **5.2.2 Calibration of oesophageal balloon for frequency response**

Testing of the frequency response is a standard procedure to ensure the balloon and the tubing system are able to respond to the different frequencies in respiration. This is to ensure that the system is not too stiff and the signal is not too dampened which could affect the accuracy of the results.

Testing of the frequency response of the balloon was done against direct response from a glass flask through a data (or signal) acquisition system “Micro 1401” (Science Products GmbH, Hofheim, Germany). The system records waveform data and can simultaneously generate waveform and digital outputs in real-time. The system was attached to a signal amplifier “1902 Amplifier” (Science Products GmbH, Hofheim, Germany) for better acquisition and illustration of the signals as per the diagram below (figure 5.1).

The software used was called “Spike” (Science Products GmbH, Hofheim, Germany), described as a life sciences data acquisition and analysis system.



**Figure 5.1: Method of Calibration of Frequency Response of oesophageal Balloon**

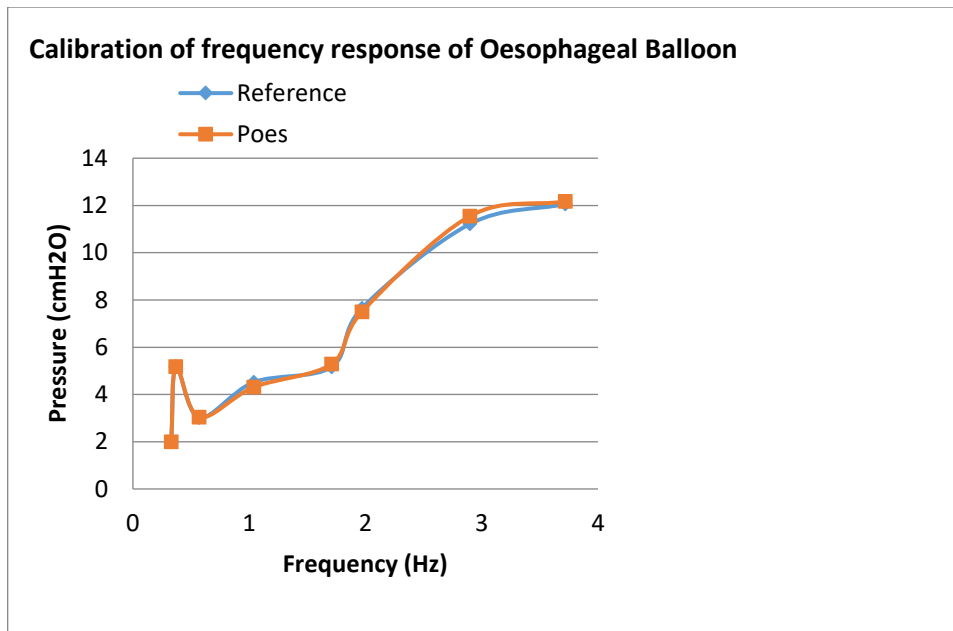
The following procedure was implemented:

- 1- A glass flask with a stopper is connected to a manometer
- 2- The oesophageal balloon is inserted into the stopper and connected to a 3 Way Tap (3WT) with a 2.5 ml syringe. The other end of the 3 WT is connected to the transducer (Validyne- Model CD12-831) to measure the pressure from the oesophageal balloon.
- 3- This is in turn connected to the data acquisition system and amplifier which connects to the monitor (figure 5.2).
- 4- Another piece of tubing (2<sup>nd</sup> tube) is inserted into the stopper (sealed with Blutak) to measure the pressure directly from inside the flask. One end is connected to a 50 ml syringe to pressurise the flask and test the frequency response (figure 5.3). The other end is connected to the transducer in the Compumedics System (figure 5.4). The transducer is connected to the data acquisition system and amplifier which connects to the monitor.

- 5- After calibration of the flask pressure with the manometer, the 2 signals from the 2<sup>nd</sup> tube and the oesophageal balloon are recorded simultaneously (Figure 5.5).
- 6- The syringe attached to the 2<sup>nd</sup> tubing is now oscillated at different speeds (Hz) and the 2 recordings are compared.
- 7- The frequency is measured at different intervals and the peak value is measured from both signals.
- 8- The values are displayed on the monitor screen, plotted (Table 5.1), and graphed (Graph 5.1).

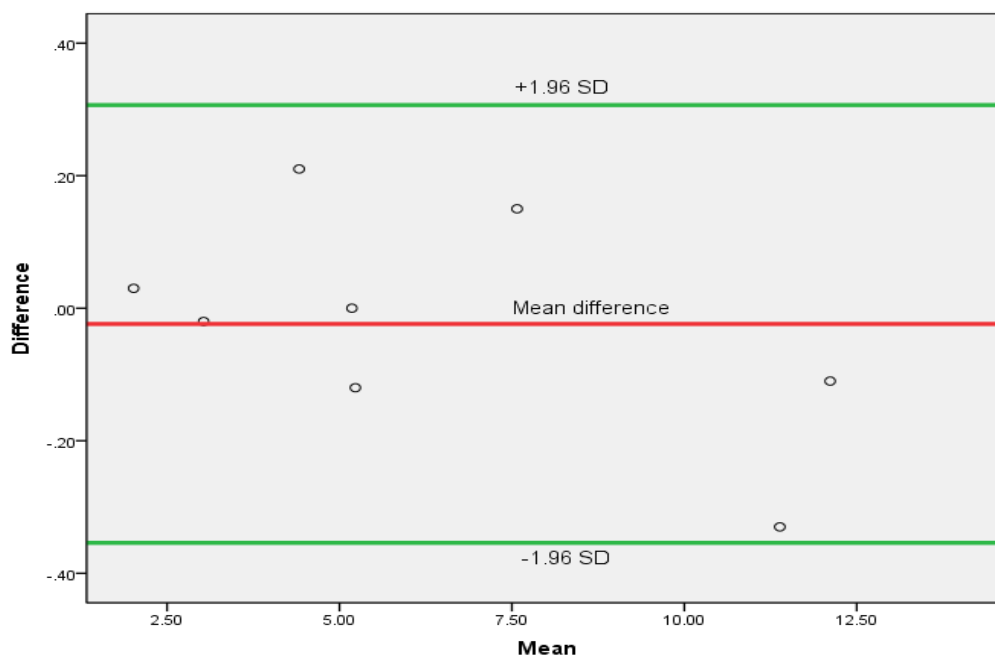
<b>Freq (N=8)</b>	<b>Reference</b>	<b>Poes</b>
<b>0.33</b>	<b>2.03</b>	<b>2</b>
<b>0.37</b>	<b>5.18</b>	<b>5.18</b>
<b>0.57</b>	<b>3.02</b>	<b>3.04</b>
<b>1.04</b>	<b>4.52</b>	<b>4.31</b>
<b>1.71</b>	<b>5.17</b>	<b>5.29</b>
<b>1.97</b>	<b>7.65</b>	<b>7.5</b>
<b>2.9</b>	<b>11.22</b>	<b>11.55</b>
<b>3.72</b>	<b>12.06</b>	<b>12.17</b>
<b>Mean ± SD</b>	<b>6.36 ± 3.66</b>	<b>6.38 ± 3.76</b>

**Table 5.1: Frequency response test values**



**Graph 5.1: Plot of pressures for frequency response test**

To ensure there was no proportional bias a Bland Altman plot was constructed and the mean difference between the two measurements was analysed against the standard deviation as set limits. The plot is demonstrated below (Graph 5.2) where there was no significant difference between the two measurements, with a mean difference of 0.025 (P=0.15).



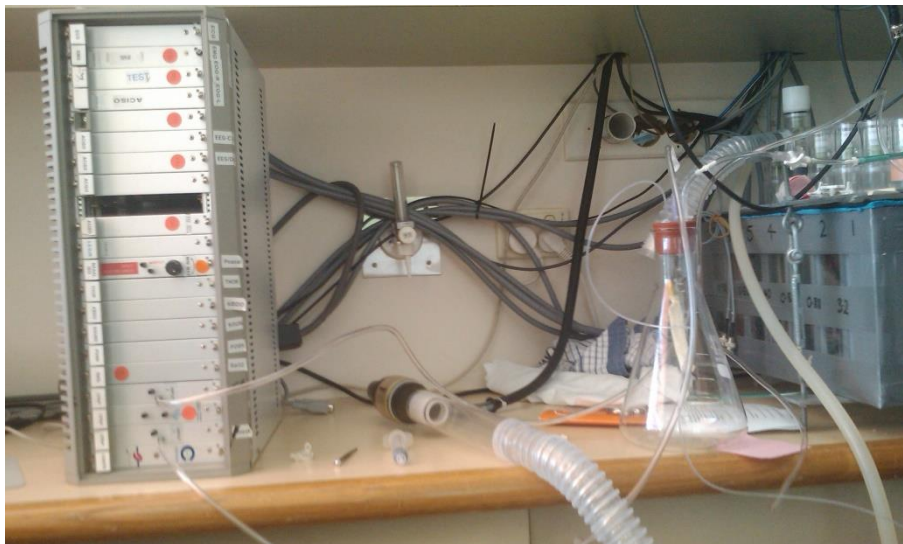
**Graph 5.2: Bland Altman Plot of Oesophageal balloon pressure Vs reference (P=0.15)**



**Figure 5.2: Validyne transducer attached to data acquisition system**



**Figure 5.3 Balloon and flask assembly**



**Figure 5.4: Flask assembly attached to Compumedics System**



**Figure 5.5: Monitor Screen showing 2 simultaneous pressure waves**

In conclusion, the calibration of the oesophageal balloon catheter system tested under different frequencies from 0.33 Hz up to 3.72 Hz showed very good correlation when compared to direct measurement from the sealed glass flask on various pressures ranging from 2-12 cm H<sub>2</sub>O. The results cover different breathing conditions for the cohort of patients who are being studied, ranging from low to high respiratory rates, as well as different intrathoracic pressures on ventilation.

## **5.3 Methods for “Measurement of intra-oesophageal pressure as a marker of respiratory effort during non-invasive ventilation in patients with extra-thoracic restrictive lung disease”**

### **5.3.1 Study population**

The participants were a subgroup of study 1. They were patients of the Victorian respiratory support service with extra-thoracic lung restriction from chest wall disease or neuromuscular disease. The main difference involved the explanation and consent for the insertion of an oesophageal balloon during the sleep studies to assess treatment effects for each condition.

Screening of the study centre database was performed. Exclusion criteria for the sub-study were applied as per “study 1” and included patients with chronic obstructive lung disease; progressive neuromuscular disease (such as motor neurone disease (MND)); a tracheostomy in situ; age less than 18 years; and being unable to obtain informed consent. Other potential participants who were further declined include those who lived outside the metropolitan area, non-English speaking patients who would have not been able to understand the details of the study and patients with significant disabilities or were too frail to travel to the study centre three times.

### **5.3.2 Enrolment**

The participants were identified from the Victorian Respiratory Support Service (VRSS) database and from the outpatients clinic per the main study. Eligible patients were then contacted by the principal investigator by telephone if they were identified from the database or discussed face to face in the outpatients department. The details of the study were fully explained similar to the main study as described above, with the

exception of providing additional information regards oesophageal balloon insertion and monitoring. The purpose of inserting the oesophageal balloon was explained and potential side effects or complications were fully addressed. The Patient Information and Consent Form (PICF) was updated to reflect the new additional information after approval from the local Ethics Committee. The new PICF included details about the process of insertion of the oesophageal balloon, as well as written details of potential discomfort of side effects.

Other details of the main study (study 1) were also discussed in detail including the randomisation process and blinding of both the participant and the investigator. Every care was taken to ensure that there was no bias towards any of the ventilation modes in the study, as the investigator explained that both modes are widely used internationally and that there was no current evidence that one mode is better than the other. This sub-study was conducted from August 2011 until November 2013.

### **5.3.3 Blinding and randomisation**

The participants were randomised as per the original protocol from the same computer-generated program by the un-blinded staff member. The blinding process remained the same with blinding of both participants and the researcher. An unblinded staff member at the centre had access to the randomisation program, filled out the sleep study information sheet and they were also responsible for allocating the ventilation mode subsequently. The randomisation mode was not mentioned anywhere on the sleep study information sheet nor in the polysomnography software entries. The overnight sleep scientist supervising the polysomnography had no knowledge of the allocated ventilation mode and they were instructed to avoid looking at the settings on the

ventilator or make any entries in the software that can compromise the process of blinding.

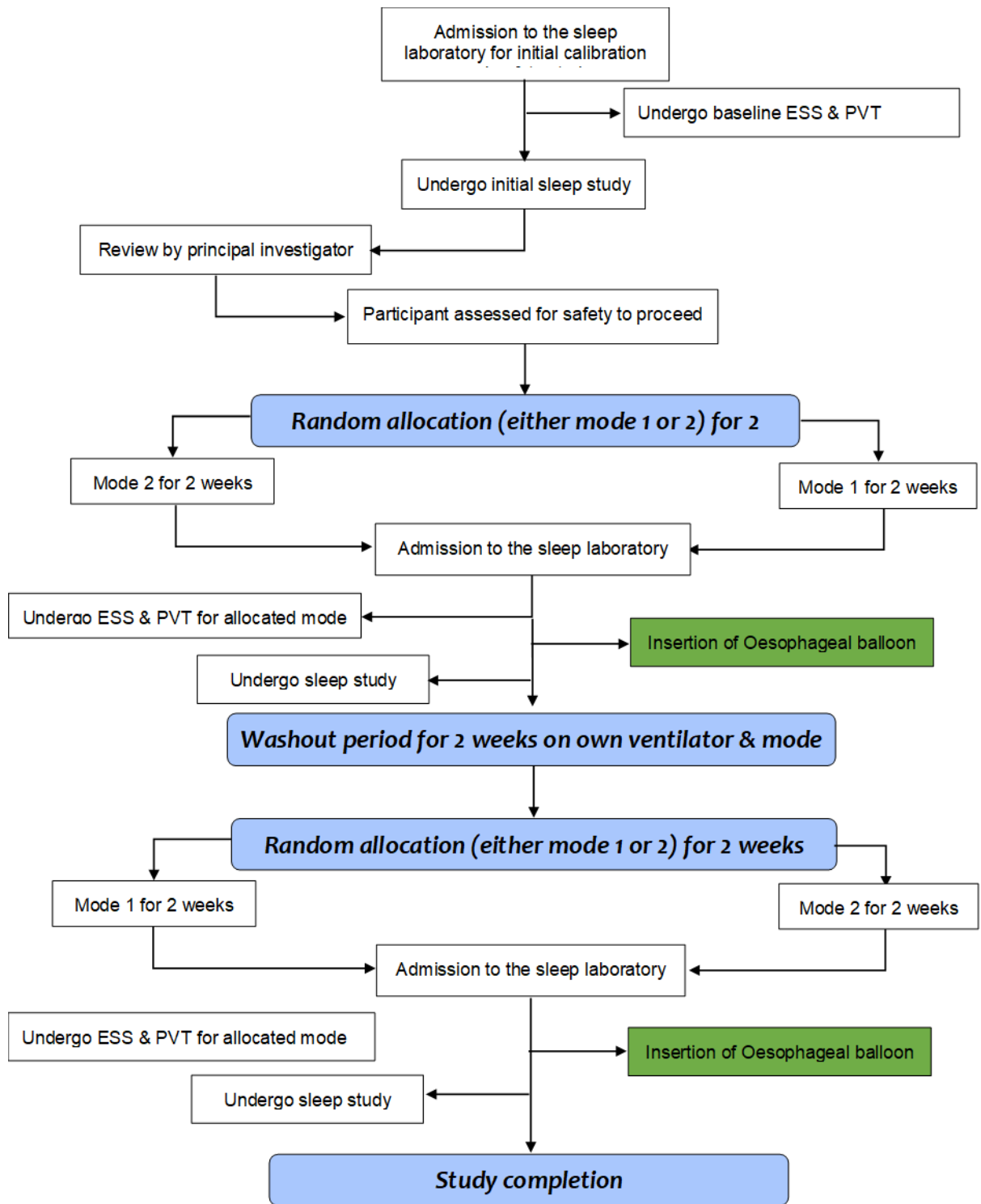
A blinded sleep scientist was responsible for sleep staging and scoring including analysis of the oesophageal balloon signal, which they were trained to assess. The scientist had no access to the randomisation mode and no information on the polysomnography software to compromise the blinding process. This scientist was not involved in any data analysis.

#### **5.3.4 Study Protocol**

The study protocol remained the same with a six-week cycle of participation in the study as per the original study (figure 5.6). All patients randomised to the sub-study had to undergo the initial calibration and safety procedure study as described above (section 2.1.2.1. The process for study randomisation and allocation of ventilation modes also remained the same (section 2.1.2.2). The only exception was the insertion of the oesophageal balloon on the nights of the second and third sleep studies in order to measure ineffective efforts on each mode of ventilation. There was no requirement for insertion of the balloon in the first sleep study which was mainly done for safety and calibration. The protocol remained the same except for the recording of additional information obtained from monitoring of the oesophageal balloon catheter system.

The oesophageal balloon was inserted through one of the two small ports in the participant mask as described below. Once the oesophageal balloon was inserted all patients were quite comfortable and not aware of its presence any more as reviewed and checked by the principal investigator. All participants seemed to tolerate the

oesophageal balloon well during sleep with no significant complications overnight or on review in the morning.



**Figure 5.6: Diagram of study 2 design and procedures**

### **5.3.5 Laboratory procedures**

The study was conducted using the same protocol as the parent study with the addition of insertion of an oesophageal balloon catheter system as per the following procedure. The participants were admitted to the sleep laboratory where they were met by the principal investigator. The purpose of the study including the insertion of the oesophageal balloon was explained including details about possible mild discomfort associated with the procedure. Before undergoing balloon insertion, the participants filled out the Epworth sleepiness scale score (appendix 1) as well the questionnaire regarding symptoms and preference (appendix 2) as per the descriptions above (section 2.2.6 and 2.2.7). They also underwent the psychomotor vigilance test (PVT) in a single room as described above (section 2.2.5.2).

The sleep study procedures were similar to study 1. A level one polysomnography protocol was followed as described above (section 2.2.5.1) with additional signals required for non-invasive ventilation including transcutaneous CO<sub>2</sub> monitoring (PtcCO<sub>2</sub>) and diaphragm EMG (d-EMG) used to assess diaphragm activity to assist in determining patient effort. An additional signal was added for scalene EMG (scEMG) also to assist in determining patient effort [222].

The oesophageal balloon was inserted as described in detail below. The polysomnography software (Compumedics Profusion 3) was programmed to acquire the signal from the oesophageal pressure. The signal was tested during spontaneous normal breathing before and after ventilation. The participant was also asked to perform manoeuvres of deep breathing during the testing to assess the signal quality. The overnight sleep scientist was shown how to troubleshoot the oesophageal signal. They were also shown how to disconnect and reconnect the balloon catheter system, in case the participant requested disconnection for bathroom breaks. A troubleshoot sheet was

provided to the overnight scientist conducting the study (appendix 4) and the principal investigator was also available on call for any troubleshooting overnight.

The participants were reviewed in the morning by the principal investigator to ensure all procedures were completed as per protocol. The participants were then implemented on the loan ventilator as set up by the unblinded staff member and discharged home on the allocated mode.

### **5.3.5.1 Principles of Measurement of oesophageal pressure**

Changes in oesophageal pressure reflect oscillations in pleural pressure and these changes can be used as an indication of respiratory effort. They do not reflect actual pressures but rather reflect the changes in pressure [3, 10, 223].

These measurements may be particularly useful in the sleep laboratory where conventional indices obtained during sleep apnoea assessment may underestimate the respiratory and sleep disturbance related to highly negative pleural pressure [224]. Oesophageal pressure measurement is the recommended method for assessing Respiratory effort related arousals (RERA) which are the main abnormalities in “Upper Airway Resistance Syndrome”, a condition that can lead to symptoms of fatigue and sleepiness[225]. These are defined; according to the American Academy of Sleep Medicine (AASM); as at least 10 seconds of increasing respiratory effort leading to an arousal from sleep when the sequence of breaths does not meet the criteria for an apnoea or hypopnoea. Although this can be determined from the nasal pressure signal and respiratory inductance plethysmography band, the use of oesophageal pressure is the preferred method as per the AASM guidelines [206]. Oesophageal balloons are also useful for measurement of respiratory mechanics particularly estimation of work of breathing as described in earlier sections (chapter 1.10).

The use of oesophageal balloon measurement as a surrogate for pleural pressure has been validated and reproduced both in recumbent and seated positions [140, 226] as well as in other positions and under different lung volumes [227]. Researchers would still need to complete the system setup with the equipment below to complete signal acquisition and perform calibration at the bedside as described below.

### 5.3.5.2 Equipment

- Balloon (Mayo Healthcare, part number 852 749), (figure 5.7)
- Thread 2.0 or 3.0 silk
- Catheter: Polyethylene tubing OD 2.08 mm, ID 1.57 mm, Product code PE208157 (on a 30m roll). (Microtube Extrusions Pty Ltd: [www.microtube.com.au](http://www.microtube.com.au)).



**Figure 5.7: Oesophageal Balloon**

- Glass flask
- Rubber stopper
- Large syringe 50ml
- Small syringe 2.5ml
- Pressure manometer

- Pressure transducer/indicator (Validyne model CD12-831)
- Bluetak to seal catheter in
- 2x Three-way taps
- Oxygen supply tubing
- Purple connector
- Barbed Luer connector: to connect the catheter to a 3-way tap.
- Output cable from pressure transducer/indicator to E-series external input box  
(Figure 5.8)



**Figure 5.8: Transducer Cable**

### **5.3.5.3 Balloon-Catheter assembly**

The catheter is cut at approximately 90 cm to allow for extra length that may be required if the end of the catheter is damaged during preparation and also to allow for additional space for patient movement at the bedside with the catheter in situ. The end of the catheter is fenestrated at a 1 cm intervals and from different angles to allow for uniform distribution of signal from the balloon through the catheter. The catheter is then inserted into the balloon leaving 1 cm gap from the end of the balloon. Using the silk thread, a hangman knot is tied at the top end of the balloon onto the catheter. The knot should not be too tight; otherwise, the catheter may be kinked or occluded. A small piece of

rubber tubing is then used to cover the knot by threading it from the free end of the catheter. We used the plastic external part of an empty ballpoint pen to help slide the small rubber piece (Figure 5.9). This process can be quite difficult and caution is required in order not to damage the balloon-catheter assembly. Once this is in place, the balloon-catheter assembly is finalised and ready for calibration.



**Figure 5.9: Rubber piece to hold the knot in place**

#### **5.3.5.4 Catheter insertion**

The procedure below was followed:

- The procedure is explained to the patient
- The patient should be sitting relaxed in bed in an upright position
- Place a small amount of 2% Lignocaine gel on the balloon.
- Measure/ estimate the distance from the nostril to the pharynx and the stomach (you can mark the tube if desired).
- Insert the balloon and advance until the balloon is situated in the pharynx
- Ask the patient to swallow a sip of water through a straw and advance while swallowing until the estimated distance.

- Look at the signal and ask the patient to sniff deeply. While in the stomach, the signal should be positive.
- Withdraw the catheter until the signal becomes negative. This indicates that the balloon is in the oesophagus. Withdraw another 10 cm roughly to position the balloon in mid-oesophagus.
- Adjust as necessary to achieve appropriate signal and subject comfort. Once in position, securely tape at the nose.
- Thread the proximal end of the catheter through the small port on the patient mask and use Bluetak to seal if necessary. This should not affect the seal of the mask.

### **5.3.5.5 Calibration of oesophageal balloon catheter system at the bedside prior to study**

The following procedure was done prior to every study when using the Oesophageal balloon:

1. Blockages in the catheter were checked for by connecting the balloon catheter assembly to a three-way tap and pushing 5ml of air into the balloon using a 5ml syringe. If there is no obstruction the balloon should fill easily without back pressure on the syringe. Backpressure in the syringe indicates blockage of the catheter, likely at the point where the balloon is secured to the catheter.
2. The proximal end of the balloon catheter assembly was threaded through the inside of the rubber stopper so that there is a distance of about 1-2 cm between the flask internal wall and the distal end of the balloon. Bluetak was used to seal the top and bottom of the rubber stopper where the catheter enters and exits the stopper, being careful not to pinch the catheter tubing.

3. The balloon-catheter-stopper assembly was placed into the flask and push the stopper down firmly to ensure a tight seal. The distal end of the catheter was connected to a three-way tap. Oxygen supply tubing was used to connect the three-way tap to the Validyne pressure transducer. A 2.5ml syringe was connected to the three way tap to insert 0.5-1ml into the balloon. The output cable from the pressure transducer was connected to channel 54 of the Compumedics external input box.
4. The pressure manometer was connected to the top of the flask stopper via oxygen supply tubing incorporating a three-way tap and purple connector (figure 5.10).



**Figure 5.10: Oesophageal Balloon Bedside Calibration**

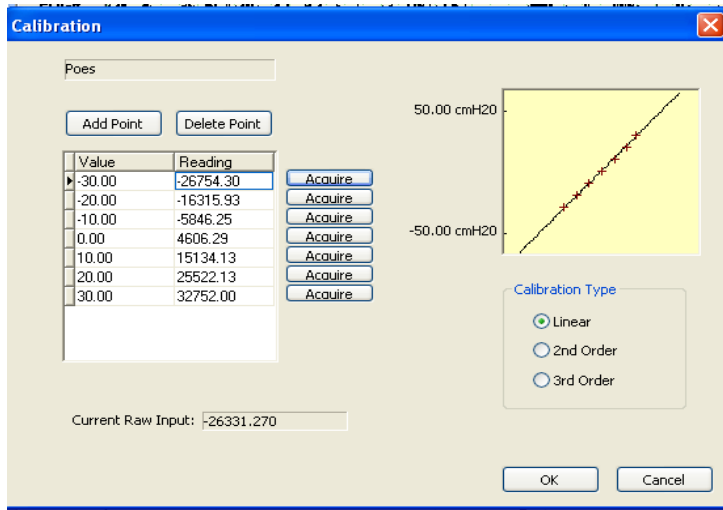
5. A study for the appropriate bed was created using the **Master\_AASM\_Poes** study configuration and the **AASM - Tx\_C\_Poes** trace layout. There was no requirement to start recording.
6. The following pressures were input into the flask-manometer circuit using a 50ml syringe in the three-way tap (Figure 5.11): 0cmH<sub>2</sub>O, -10 cmH<sub>2</sub>O, -20 cmH<sub>2</sub>O, -30 cmH<sub>2</sub>O, +10 cmH<sub>2</sub>O, +20 cmH<sub>2</sub>O, +30 cmH<sub>2</sub>O. NB. For negative

pressures, the oxygen supply tubing was connected to the rear port at the top of the manometer. The pressure output to the Compumedics equipment was verified by viewing the output in the meter box at the bottom of the screen in the PSG software.

7. If the output was not within  $\pm 2$  cmH<sub>2</sub>O, recalibration was required. If recalibration was required, the calibration window was accessed with a right-click on the Poes channel label and then 'calibrate' was selected. The pressures were entered as above and for each pressure acquired and the associated output was recorded against it (see below calibration plot). Proceeding with Poes measurement was only undertaken if there was good calibration as below (Figure 5.12).



**Figure 5.11: 50ml Syringe to pressurise Flask with balloon assembly**



**Figure 5.12: Calibration figures and plot at the bedside**

### 5.3.6 Endpoints

The **primary outcome** for this sub-study was the number of ineffective efforts per hour as seen by a negative deflection from baseline signal in the oesophageal balloon pressure trace (Poes) with no associated ventilator breath, on each mode.

The **secondary outcome** was poor triggering as evidenced by dys-synchrony between the ventilator and the patient's efforts (shown by activity in the oesophageal balloon "Poes", scalene "ScEMG", and diaphragm "d-EMG" signals), expressed as total time in seconds. It represented periods where the ventilator rate was asynchronous with the patient effort as evidenced by these signals and were less than 10 seconds per period (otherwise would be labelled as a central event).

### **5.3.7 Data Collection and statistical analysis**

The primary investigator collected all data; including sleep and ventilation parameters, ineffective efforts and poor triggering; which were entered into excel sheets where the treatment arm was blinded by the allocated code. After analysis of the sleep studies by the dedicated scientist, the data were exported from the Compumedics software to a separate excel sheet.

The data were then prepared for clean export into the statistical software by the principal investigator. All data were analysed by using the software “IBM SPSS version 23”. Data were displayed as mean and median values with standard deviation or confidence intervals. Statistical significance was set at 0.05 for all analyses. The study was conducted as a self-controlled cross over study to improve the study power and minimise the impact of confounding factors and co-variables. The study was designed to detect a difference of 40 ineffective breaths per hour with a standard deviation of 20 based on previous studies[135]. 8 patients are required to have an 80% power to find such a difference at an alpha of 0.05. Log transformation was required for analysis as the data were skewed and the number of observations did not allow a non-parametric test to be performed. The results were confirmed by Friedman’s ANOVA as further exploratory analyses. Linear regression analysis was performed to test the effect of ineffective efforts on sleep and ventilation parameters.

All statistical analyses were performed by the principal investigator while blinded.

## **Chapter 6**

### **6 Results of study 2 “measurement of intra-oesophageal pressure as a marker of respiratory effort during non-invasive ventilation in patients with restrictive lung disease”**

In this sub-study, where all newly recruited participants had to tolerate the insertion of an oesophageal balloon twice in the second and third sleep studies, recruitment became even more difficult than study 1. Despite extensive explanation of the procedure of inserting the balloon-catheter device, including the use of local anaesthesia, most potential participants declined to have this relatively invasive procedure whilst awake.

#### **6.1 Participants**

Six patients out of 16 participants in the main study (chapter 2) were recruited and consented for the sub-study. Only five participants completed the randomisation, as the last recruited patient withdrew from the study after arriving to the sleep laboratory (figure 6.1).

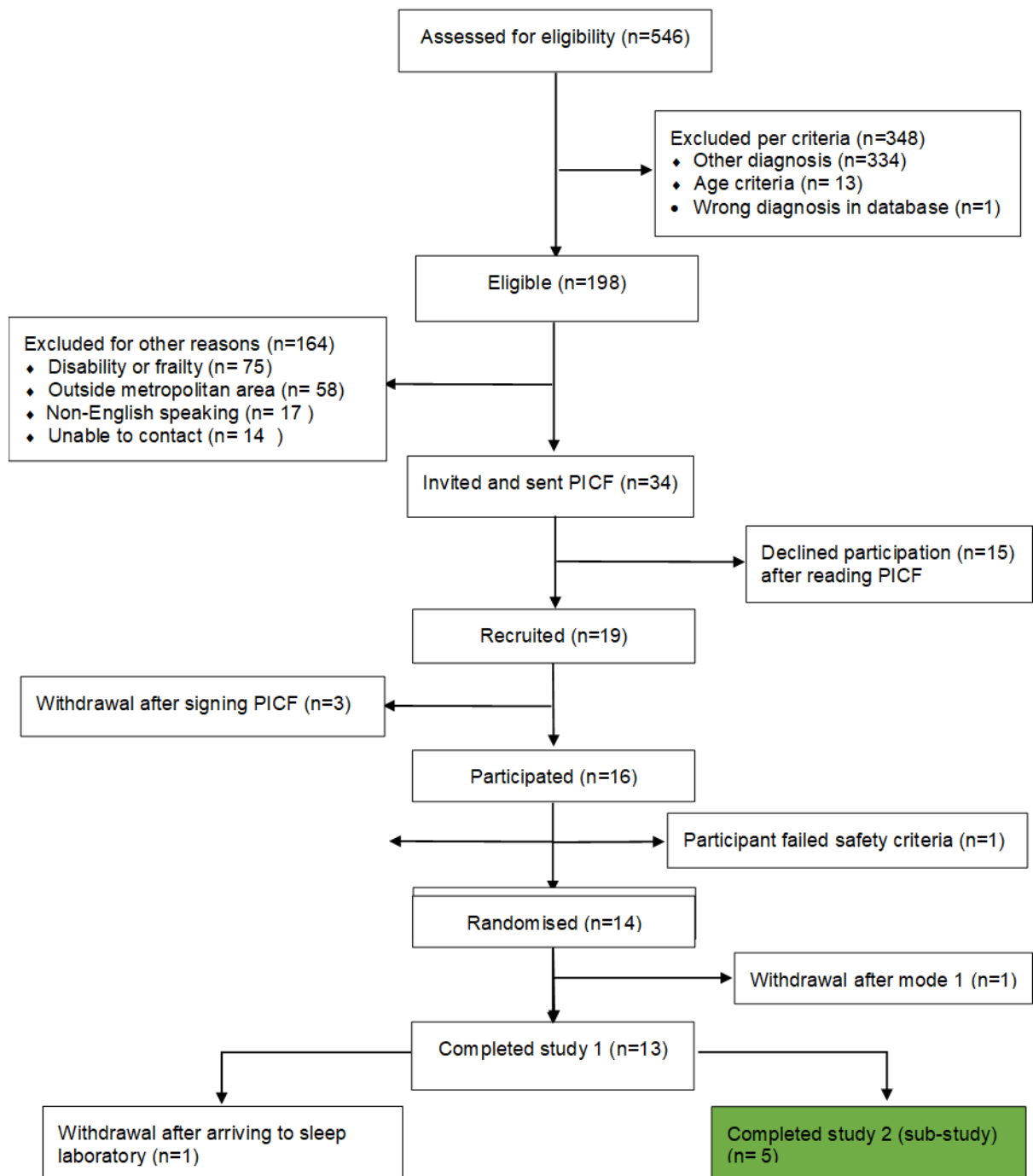
Although the insertion of the oesophageal balloon was slightly uncomfortable, all participants tolerated it well with no significant side effects except for one participant who experienced mild nausea that settled within a few minutes. As the oesophageal balloon-catheter system was threaded through one of the small ports on the patients' masks, no compromise of mask seal was experienced due to its insertion. There was no obvious impact on ventilation parameters due to the good

seal achieved. This was checked by reviewing the leak signal in the polysomnography software but also by ensuring that adequate volume delivery was achieved on the ventilator.

Four out of the five participants who completed this study had chest wall disease due to kyphoscoliosis. The remaining subject had undifferentiated myopathy. The participants had been on non-invasive ventilation for some time with a mean of  $3.2 \pm 3.3$  years. They were all on pressure control ventilation via VPAP 3 or 4 ST. The patient demographics for this sub-study are displayed below (table 6.1).

<b>Age</b>	<b><math>61.4 \pm 14.7</math></b>	<b>years</b>
<b>BMI</b>	<b><math>29.9 \pm 8</math></b>	<b>kg/m<sup>2</sup></b>
<b>Weight</b>	<b><math>78.8 \pm 23.9</math></b>	<b>kg</b>
<b>FEV1</b>	<b><math>1.14 \pm 0.38</math></b>	<b>litre</b>
<b>VC</b>	<b><math>1.50 \pm 0.63</math></b>	<b>litre</b>
<b>MIP%</b>	<b><math>37 \pm 7</math></b>	<b>cm H<sub>2</sub>O</b>
<b>MEP%</b>	<b><math>70\% \pm 27</math></b>	<b>cm H<sub>2</sub>O</b>
<b>IPAP</b>	<b><math>21 \pm 4</math></b>	<b>cm H<sub>2</sub>O</b>
<b>EPAP</b>	<b><math>9 \pm 4</math></b>	<b>cm H<sub>2</sub>O</b>
<b>RR</b>	<b><math>18 \pm 2</math></b>	<b>BPM</b>
<b>Male, female</b>	<b>n=5, n=0</b>	
<b>CWD, NMD</b>	<b>n=4, n=1</b>	

Table 6.1: Patient demographics for the sub-study (study 2)



**Figure 6.1 CONSORT Flow diagram of participation in the sub-study (study 2)**

PICF = patient informed and consent form

The main outcome in this study was to compare the number of ineffective efforts as seen by a more negative deflection in the oesophageal balloon signal from the baseline signal without an associated ventilator breath (figure 6.2).

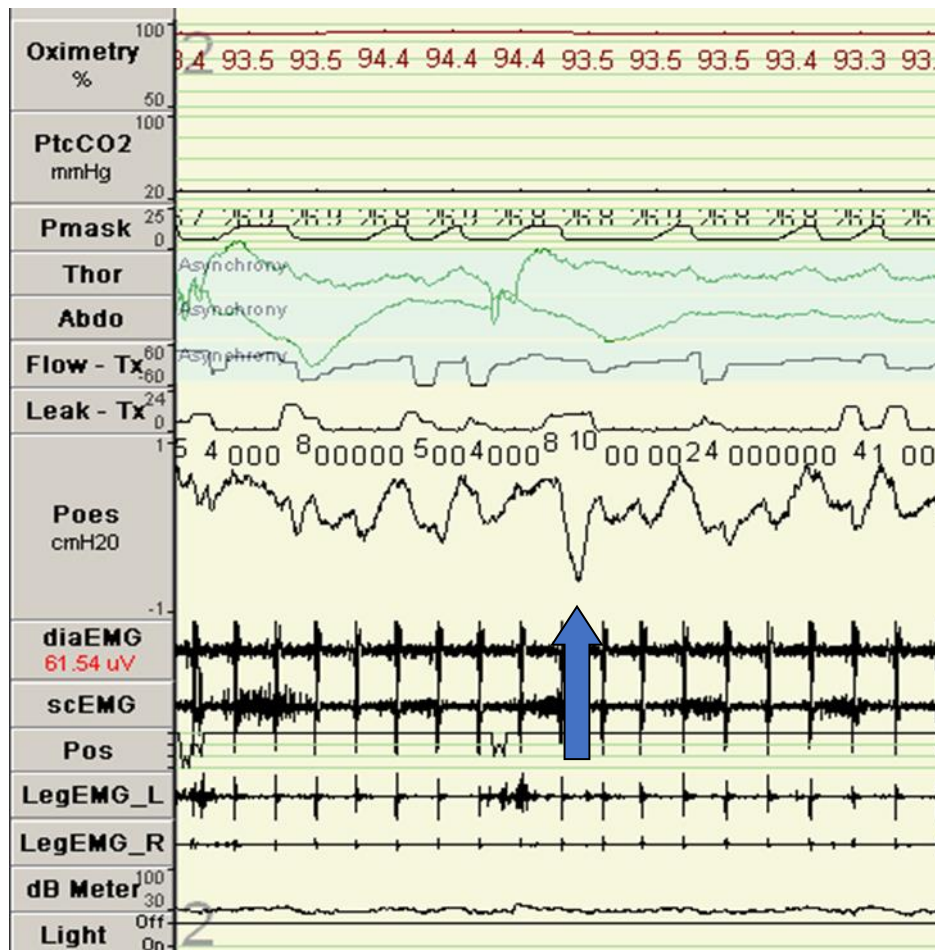


Figure 6.2: Ineffective effort represented by the arrow in the figure

## 6.2 Results for ineffective efforts and poor triggering

For ineffective efforts, the data were logged (LogN transformation) to correct for abnormal distribution which was positively skewed, with the addition of + 0.1 to correct for zero values. A paired t-test was then possible to compare the frequency of ineffective efforts between the two different modes, as the data was no longer positively skewed and fitted the test of normality. The geometric mean value for

ineffective efforts in the Spontaneous Mode (S) was  $11.44 \pm 25.64$  events per hour. There were no ineffective efforts in the Spontaneous Timed Mode (ST) with a geometric mean value of  $0.1 \pm 1$  events per hour. The spontaneous timed mode was superior to the spontaneous mode with a mean difference of  $11.43 \pm 24.64$  (95% confidence interval: 1.84 – 5813.53, P 0.033), (Table 6.2).

Parameter	S Mode	ST Mode	t-test	Significance
	Geometric Mean (SD)	Geometric Mean (SD)	Mean Diff (SD) = S-ST	P value
Ineffective efforts / hr	11.44 (25.64)	0.1 (1)	11.43 (24.64)	<b>0.033</b>

**Table 6.2: Paired t-test for ineffective efforts (Log transformation), (n=5)**

SD= Standard deviation, hr = hour

The significant result was confirmed by doing exploratory analysis (non-parametric analysis of variance or “Friedman’s ANOVA” (Appendix 5, Table A.13).

Poor triggering as evidenced by dys-synchrony between the ventilator and the patient’s efforts (shown by activity in oesophageal balloon pressure “Poes”, scalene “ScEMG”, and diaphragm “d-EMG” signals), was also assessed as a secondary outcome in this sub-study. The results are expressed as time in seconds. The mean value for S mode was  $1224 \pm 2223$  seconds, while for ST mode it was 0. As the data were positively skewed, log transformation was used for analysis with paired t-test. There was no statistically significant result between the 2 modes (P 0.181), (Table 6.3).

Parameter	S Mode	ST Mode	t-test	Significance
	Geometric Mean (SD)	Geometric Mean (SD)	Mean Diff (SD) = S-ST	P value
Poor triggering (sec)	1224 (2223)	0.1 (1)	1224 (2222)	0.18

**Table 6.3: Paired t-test for poor triggering (Log transformation) (n=5)**

SD= Standard deviation, Sec= Seconds

Similar to ineffective efforts the results of the paired t-test were confirmed by further exploratory analysis to test the relationship between the mode of ventilation and poor triggering by Friedman ANOVA and there was no significant correlation (Appendix 5, Table A.14).

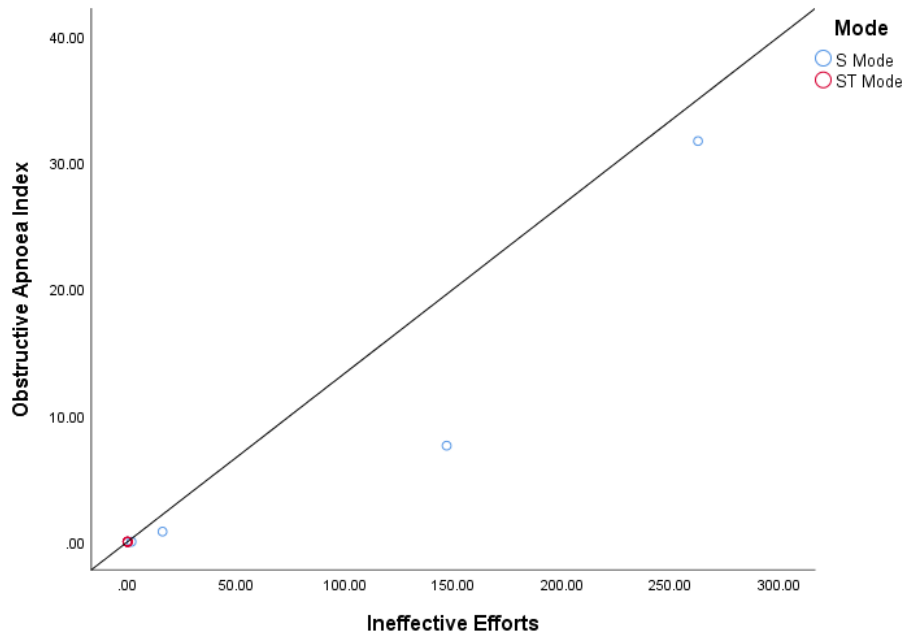
Finally, linear regression analysis was performed to assess the effect of the presence of ineffective efforts on sleep and ventilation parameters.

With regards to sleep quality, there was a significant negative correlation between the presence of ineffective efforts and better sleep efficiency ( $r .716$ ) and the regression model predicted 51% of the variance. The model was a good fit for the data ( $F 8.4, P 0.02$ ).

There was no significant correlation between ineffective efforts and the total sleep time ( $r .55$ ) and the regression model predicted 31% of the variance, ( $F 3.5, P 0.098$ ). There was also no significant correlation between ineffective efforts and the number of awakenings ( $r .54$ ) and the regression model predicted 29% of the variance ( $F 3.24, P 0.11$ ).

Regarding the effect of ineffective efforts on respiratory events, there was a positive correlation for a number of parameters. There was a very strong correlation between

ineffective efforts and the total Obstructive Apnoea Index (OAI) ( $r .957$ ) and the regression model predicted 91% of the variance. The model was a very good fit for the data ( $F 86.267, P 0.000015$ ), (Graph 6.1).

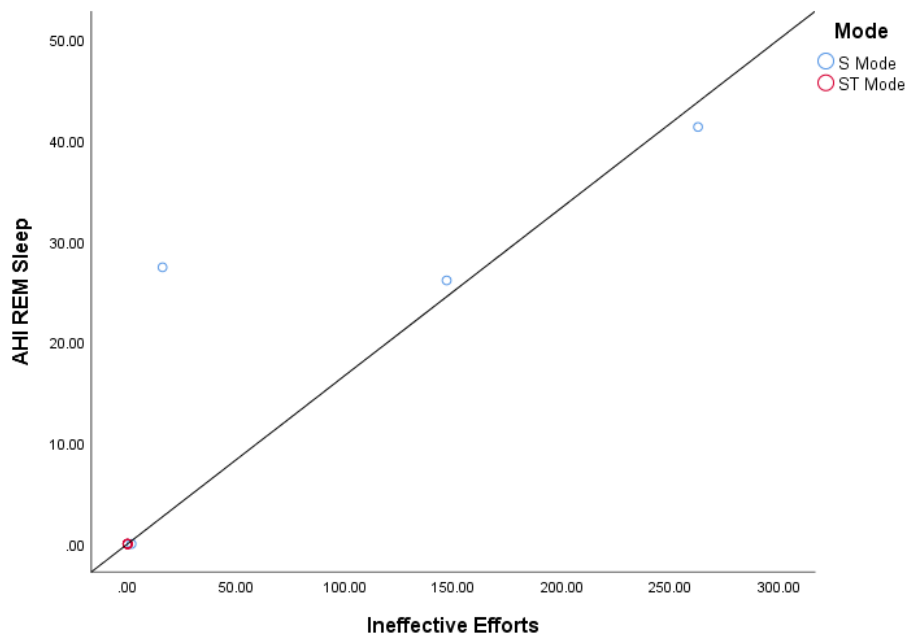


**Graph 6.1: Linear regression between ineffective efforts and Obstructive Apnoea Index (OAI)**

There was also a strong correlation between the presence of ineffective efforts and the total Mixed Apnoea Index (MAI) ( $r .859$ ) and the regression model predicted 74% of the variance. The model was a very good fit for the data ( $F 22.521, P 0.001$ ), (Graph 6.2).

On the other hand, there was no significant correlation between ineffective efforts and the total Central Apnoea Index (CAI) ( $r .052$ ) and the model did not fit well ( $F .021, P 0.887$ ), (Graph 6.18).

The total Apnoea Hypopnoea Index in REM sleep (AHI REM Sleep) correlated well with the presence of ineffective efforts ( $r .869$ ) and the regression model predicted 75% of the variance. The model was a very good fit ( $F 24.578, P 0.001$ ), (Graph 6.2).



**Graph 6.2: Linear regression between ineffective efforts and Apnoea Hypopnoea Index in REM sleep (AHI REM Sleep)**

This was not replicated for the AHI in non-rapid eye movement sleep (NREM) sleep ( $r = .57$ ) with ( $F = 3.762$ ,  $P = 0.088$ ).

For the total Apnoea Hypopnoea Index (AHI) in all phases, there was a near statistically significant correlation between the presence of ineffective efforts and the AHI ( $r = .613$ ), predicting 38% of the variance ( $F = 4.815$ ,  $P = 0.06$ ).

Finally, we tested the model with poor triggering to see if there is a correlation between this and ineffective efforts. There was no significant correlation ( $r = .188$ ) and the model did not fit well ( $F = .293$ ,  $P = 0.603$ ).

### **6.3 Discussion:**

This physiological sub-study aimed to determine whether there was a difference between spontaneous mode and spontaneous timed mode non-invasive ventilation in triggering the ventilator and the impact on synchrony between the machine and the patient.

The results of the sub-study showed that there were less ineffective efforts on spontaneous timed mode than spontaneous mode; however, there was no significant difference in the overall time of poor triggering. There was also a significant correlation between the presence of ineffective efforts and sleep quality, the mixed apnoea index and the obstructive apnoea index. On the other hand, there was no significant correlation with total sleep time, the number of awakenings and the central apnoea index.

Failure to trigger the ventilator can occur in patients with chest wall and neuromuscular disease due to upper airway obstruction, respiratory muscle weakness, or the presence of significant leak. The patients may also fail to trigger the ventilator due to reduced ventilatory drive.

The presence or absence of ineffective efforts leading to failure to trigger the ventilator is best assessed by the insertion of an oesophageal balloon, a surrogate measure for intra-pleural pressure [3, 10, 223]. A negative deflection in the pressure signal indicates an effort by the patient to breathe and when not followed by a triggered breath; this reflects a failure to trigger the ventilator. Although cumbersome and slightly uncomfortable for an awake patient, it is the best available and most validated method of assessing ineffective efforts.

The number of ineffective efforts in the spontaneous mode was much higher than in the spontaneous timed mode. Some of the possible reasons include matching of the

patient's respiratory effort with the ventilator rate, wherein this study centre it is usually set a couple of breaths under the intrinsic rate of the patient. Other reasons include adjusting the minimum and maximum inspiratory time to be within a more physiological window. In the spontaneous mode, these settings were set at the minimum and maximum allowance (0.1 and 4 seconds respectively). This can result in either very small breaths if the ventilator cycles to expiration quickly due to the inspiratory time being too short, or the opposite where the ventilator fails to cycle into expiration in time due to a prolonged inspiratory time.

The results of this research were reasonably similar to a previous study by Fanfulla et al., where suboptimal ventilator settings in patients with neuromuscular disease resulted in an increased number of ineffective efforts [135]. The authors in the study compared two settings of ventilation, one based on clinical assessment, which they called usual, and the other was labelled as physiological based on assessment of the patient's respiratory effort. The study was conducted with non-invasive pressure support ventilation similar to this study. To assess the patients' respiratory effort, an oesophageal balloon was inserted and respiratory mechanics were measured. The patients were monitored with polysomnography for two consecutive nights in random order of each setting. Ventilatory and sleep parameters were measured as an outcome. The results of the study showed that physiological titration of non-invasive ventilation was associated with better gas exchange, sleep efficiency and percentage of rapid eye movement sleep (REM). There was a significant correlation between the improvement in these parameters and the reduction in ineffective efforts [135]

The results of this sub-study showed that there was a significant correlation between the presence of ineffective efforts and sleep quality as reflected in sleep efficiency. This is again similar to the study by Fanfulla et al., where the reduction in ineffective efforts

resulted in better sleep efficiency [135]. This may be a reason for the improved level of sleepiness seen in our study.

Addressing patient-ventilator asynchrony has been recognised not just to improve sleep efficiency but also having an impact on patient adherence to therapy. In the study by Hannan et al., patients with respiratory failure were randomised to start on either daytime ventilation or polysomnographic titration according to a standard protocol. The aim of the study was to assess whether the latter was associated with less patient-ventilator asynchrony. The study population was heterogeneous and included a number of conditions with the majority being motor neuron disease, but also included some patients with stable neuromuscular disease and chest wall disease. The results of the study confirmed that there were fewer patient-ventilator asynchrony events in the polysomnographic group than the daytime group. In patients who had poor adherence, polysomnographic titration improved their adherence to therapy by more than one hour [180].

Similarly, in the study by Georges et al., where the authors assessed the presence of upper airway obstruction in patients with amyotrophic lateral sclerosis (ALS), there was a negative impact on survival in patients who had untreated obstructive sleep apnoea [49]. Although this was a different group of patients with generally shorter survival than the cohort of patients in this study, it highlights the importance of optimising ventilation with appropriate ventilator settings.

There are not many other clinical studies in this outpatient group of extrathoracic lung disease patients; however other studies conducted in the acute setting in the intensive care unit; showed that ineffective triggering and dys-synchrony were associated with prolonged duration of mechanical ventilation [188].

There was also a significant correlation with the number of respiratory events particularly the obstructive apnoea index and the mixed apnoea index; however, there was no significant correlation with the central apnoea index. The overall AHI in REM sleep correlated with the presence of ineffective efforts; however, this was not the case in NREM sleep. The overall AHI for all phases of sleep almost reached a statistically significant correlation (P 0.06) with the number of ineffective efforts. The reduction in the number of respiratory events, in addition to the reduction in ineffective efforts, were likely major contributing factors to better quality sleep in the Spontaneous Timed mode. On the other hand, there was no statistically significant difference in the time spent with poor triggering and this may be secondary to the small number of participants in the sub-study which was underpowered to detect a significant difference. The other likely reason is that this sub-study did not particularly target optimising synchrony, in contrast to the other studies by Fanfulla and Hannan [135, 180]

In conclusion, our results indicate that ST mode was associated with less ineffective efforts, which contributed to better sleep efficiency and correlated well with fewer respiratory events. There was no significant difference in the effect of ineffective efforts on poor triggering. This study and the work of other authors as above highlight the importance of attempting to optimise non-invasive ventilation to improve patient outcomes such as improved sleep quality, sleepiness and adherence. Larger and longer-term studies including multicentre trials are required to address long term health benefits and effects on mortality in these patients. Studies addressing the effect on healthcare costs are also important to undertake.

## Chapter 7

### 7 Study 1 and 2 limitations

The study design was a randomised controlled double-blind cross over study that involved a main study (study 1) and a sub-study (study 2) over a six-week period.

The main study had a number of limitations. Firstly, the study did not reach the target participant numbers due to difficulty in recruitment, hence the study was underpowered for some of the outcomes. The failure to achieve the appropriate sample size was due to a number of factors. The patients had to reside in a metropolitan area rather than rural and remote areas to be able to attend the study centre three times in a six-week period. Patients who were quite frail or have a disability were also not suitable for the study. Patients from non-English speaking background were excluded as would have had difficulty understanding the study protocol and do an informed consent.

The second limitation is that this study involved a limited cohort of patients, particularly that there were only two patients with neuromuscular disease at the end of recruitment. It is possible that this is due to the fact that neuromuscular disease patients are generally frailer and have more disabilities due to muscle weakness. This limits the generalisability of the study, as ideally more patients in this group should have been recruited.

The third limitation is that the study was conducted over a six-week period with two weeks as a washout period. This may have not had enough time to have a significant impact on gas exchange particularly due to the small sample size but also the fact that these patients were already receiving treatment with ventilation. It can also take up to three months to see improvements in arterial carbon dioxide level (PaCO<sub>2</sub>) as

demonstrated in the trial by Howard et al., which compared CPAP to non-invasive ventilation in obesity hypoventilation syndrome [88].

The fourth limitation is that the study population were stable patients already on non-invasive ventilation mostly spontaneous timed mode. To study the effect of treatment, such as mode of ventilation on a group of patients, ideally, de novo patients naïve to this form of therapy rather than patients who are already established on treatment should be recruited; however, this was not practical in a single centre study to achieve the appropriate sample size due to the challenges mentioned above. The fact that the patients were already familiar with ventilation, particularly the spontaneous timed mode, could have affected some of the results and created bias. This is particularly relevant in the questionnaires regarding the Epworth sleepiness scale and the symptom and preference scores. It is also possible that the two weeks on ventilation for reach mode may have not been long enough to see an effect on functional assessment of psychomotor skills. Previous studies that showed positive outcomes in these two measures were conducted over longer periods [88, 156, 157]. Longer studies may be required to test these outcomes, although recruitment may be difficult for a similar design. The study was also limited in neurocognitive assessment to only psychomotor vigilance testing. This was difficult to establish also in previous studies involving CPAP therapy, a relatively similar form of ventilation [219, 220]; however, one study comparing CPAP to bilevel ventilator support in patients with obesity hypoventilation syndrome, showed improvement in some aspects of psychomotor vigilance testing [86]. Other cognitive assessments may have been valuable and complementary in this research study.

In the sub-study, an oesophageal balloon was inserted in five out of the 13 patients to assess for ineffective efforts and poor triggering. In addition to the above limitations in

the main study, there were other challenges. Patient recruitment was even more difficult due to the invasive nature of the balloon insertion procedure, which had to be done twice

whilst the patients were awake. It was not possible to perform this procedure while the participants were sedated, as this would have been unsafe in a ward environment, in contrast to other studies done in the intensive care unit where sedation can be administered safely or is already running.

The study was underpowered to detect any significant results for poor triggering. The study design was also not targeting optimising of synchrony on either mode which would have affected the outcome.

Other limitations in the sub-study include occasionally obtaining sub-optimal signals from the oesophageal balloon during the course of the night. It was not possible to manipulate the balloon catheter system again during sleep as this would have woken the patients up, in addition to possibly causing discomfort. This may have underestimated the difference between the two modes in some of the physiological outcomes.

Despite the above limitations, we found statistically significant results in a number of parameters. There was an improvement in overnight oxygenation, an important parameter in ventilation outcomes, on spontaneous timed mode than on spontaneous mode. There was also significant improvement in the number of respiratory events overnight, including the total apnoea hypopnoea index, on spontaneous timed mode when compared to spontaneous mode. Total sleep time was also better on spontaneous timed mode than spontaneous mode. Physiological assessment using an oesophageal balloon revealed that there were less ineffective efforts that correlated well with improvement in some of the respiratory and sleep parameters.

## 8 Conclusion

This thesis compared the impact of two important modes of ventilation that are commonly used in patients with extra-thoracic lung restriction. We aimed to study the effect on ventilation efficacy, and sleep efficiency. We also assessed the interaction between the patient & ventilator from a physiological endpoint using an oesophageal balloon as a measure for ineffective efforts and dys-synchrony. Importantly we compared the two modes effect on the patient with regards to the level of sleepiness, psychomotor skills and patient preference. There is very little research in the literature in this area and there no head to head trials with a similar design comparing the two modes.

The study is important not only in establishing which mode is superior and more effective but also to prevent complications associated with sub-optimal ventilation. As outlined from the literature review and comparison with other studies, untreated or suboptimally treated respiratory failure has deleterious effects on patients. The patients suffer from dyspnoea, poor quality sleep, headaches and poor neurocognitive function. Suboptimal treatment also results in more frequent hospital admissions which not only has serious implications for the patients, but also significant cost effects for the healthcare system. Complications of suboptimally treated respiratory failure include pulmonary hypertension and congestive cardiac failure, both of which significantly worsens the prognosis in these patients. By providing effective non-invasive ventilation, the studies have repeatedly and consistently shown that it reverses respiratory failure and improves quality of life. There was also a survival benefit in small groups of patients, who generally have shorter life expectancy such as motor neurone disease patients [47]. Although improved survival has not been established in

other groups of patients, this is possibly secondary to a lack of appropriate long-term studies in these types of patients and more research in this area is still required.

The results of this research showed a significant difference in ventilation efficacy with better overnight oxygenation on Spontaneous Timed (ST) mode than Spontaneous (S) mode; however, there was no difference between the two modes in CO<sub>2</sub> measurements.

The study was underpowered to detect a significant difference in the level of hypercapnia between the two modes, which may relate to the fact that the patients were clinically stable and already receiving ventilation, but it is also possible that the duration of the study was too short to show such difference.

The study showed that respiratory events were less frequent for most parameters on ST mode compared to S mode. This may be explained by the inability of these patients to trigger the ventilator properly on spontaneous mode, due to their compromised respiratory mechanics, muscle weakness and upper airway obstruction.

Sleep parameters also improved on ST mode compared to S mode with better overall sleep time and near significant sleep efficiency. There was no significant difference in the number of awakenings between the two modes. These results were comparable to previous work which showed that physiological optimal implementation of non-invasive ventilation was associated with better sleep quality [135].

From a physiological point of view, Spontaneous Timed mode improved ineffective patient efforts on ventilation, there were also fewer problems with triggering on Spontaneous Timed mode, although this did not reach statistical significance. This was likely due to the fact the study was underpowered, but also that adjusting the ventilator to optimise synchrony was not one of the aims of this study. The reduction in ineffective efforts correlated well with improved sleep efficiency and reduction in respiratory events. Previous work by other authors has shown that optimising synchrony is not only

associated with better ventilation and sleep parameters but also improves adherence to therapy in patients who were not previously adherent [180].

In patients with chronic stable ventilatory failure, Spontaneous Timed mode ventilation was superior to Spontaneous mode in improving nocturnal ventilation, respiratory events and some sleep parameters. These improvements appear to be mediated by a reduction in ineffective patient respiratory efforts in the ST mode. There was also a non-significant trend towards improvement in triggering and patient preference with spontaneous timed mode. There was no difference in psychomotor function between the two modes of ventilation. This suggests that although subjective sleepiness was improved with ST mode ventilation, the improvements in sleep may not have been sufficient to impact daytime function, although the study duration or power may not have been adequate for the changes in sleep to be reflected in daytime function.

Based on the results of this and previous studies study, spontaneous timed mode is recommended over spontaneous mode in patients with neuromuscular disease and chest wall disease. The long-term effects of these ventilation modes on patient outcomes and mortality in this population are not known. Further studies are required to assess whether the results of this study are applicable to other conditions. The use of oesophageal balloons in evaluating ineffective efforts is quite useful and remains the gold standard, but is not practical to be used routinely and will remain limited to research studies.

There are still many gaps in this area with a real need for good quality research.

Longer studies with greater power are required to determine whether the outcome of this research translates into long term health benefits, such as reduction in hospital admissions or mortality, as well as improvement in daytime physical and cognitive

function. Future studies are also required to address the cost-effectiveness of this treatment.

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## **Appendices**

### **Appendix 1: Epworth Sleepiness Scale**

**For Treatment A: Please fill out the table below regarding the last 2 weeks: How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:**

**Scale:**

**0 = no chance of dozing**

**1 = slight chance of dozing**

**2 = moderate chance of dozing**

**2 = high chance of dozing**

SITUATION	CHANCE OF DOZING
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (e.g. a theatre or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____

**Total Score** \_\_\_\_\_

**Epworth Sleepiness Score. Jones MW A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991 14:540-5**

**Appendix 2: Participant Questionnaire**

**Project: Spontaneous versus spontaneous timed mode of assisted ventilation in patients with chest wall disease and stable neuromuscular disease**

**Please answer the following questions regarding Mode A (first 2 weeks):**

**A- Compared to your usual ventilator, how do you rate your breathing comfort on these settings? Please circle the most appropriate answer**

**1. Much worse    2. Worse    3. No different                      4. Better            5. Much better**

**B- Compared to your usual daytime activity, how do you rate your level of energy during daytime? Please circle the most appropriate answer**

**1. Much worse    2. Worse    3. No different                      4. Better            5. Much better**

**C- Compared to your usual, how do feel with regards to feeling fresh in the morning? Please circle the most appropriate answer**

**1. Much worse    2. Worse    3. No different                      4. Better            5. Much better**

**D- Compared to your usual circumstances, have you been experiencing any unusual morning headaches? Please circle the most appropriate answer**

**Yes**

**No**

**If Yes, Please circle the most appropriate answer**

**1. Much worse   2. Worse   3. No different   4. Better   5. Much better**

**E- Compared to your usual night sleep on your ventilator, how do you rate your quality of sleep? Please circle the most appropriate answer**

**1. Much worse   2. Worse   3. No different   4. Better   5. Much better**

**Participant Questionnaire**

**Project: Spontaneous versus spontaneous timed mode of assisted ventilation in patients with chest wall disease and stable neuromuscular disease**

**Please answer the following questions regarding Mode B (Second 2 weeks):**

**A- Compared to your usual ventilator, how do you rate your breathing comfort on these settings? Please circle the most appropriate answer**

**1. Much worse    2. Worse    3. No different                      4. Better            5. Much better**

**B- Compared to your usual daytime activity, how do you rate your level of energy during daytime? Please circle the most appropriate answer**

**1. Much worse    2. Worse    3. No different                      4. Better            5. Much better**

**C- Compared to your usual, how do feel with regards to feeling fresh in the morning? Please circle the most appropriate answer**

**1. Much worse   2. Worse   3. No different                      4. Better           5. Much better**

**D- Compared to your usual circumstances, have you been experiencing any unusual morning headaches? Please circle the most appropriate answer**

**Yes**

**No**

**If Yes,                      Please circle the most appropriate answer**

**1. Much worse   2. Worse   3. No different                      4. Better           5. Much better**

**E- Compared to your usual night sleep on your ventilator, how do you rate your quality of sleep? Please circle the most appropriate answer**

**1. Much worse   2. Worse   3. No different                      4. Better           5. Much better**

**For Treatment B: Please fill out the table below regarding the last 2 weeks: How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:**

**Scale:**

**0 = no chance of dozing**

**1 = slight chance of dozing**

**2 = moderate chance of dozing**

**3 = high chance of dozing**

<b>SITUATION</b>	<b>CHANCE OF DOZING</b>
<b>Sitting and reading</b>	_____
<b>Watching TV</b>	_____
<b>Sitting inactive in a public place (e.g. a theatre or a meeting)</b>	_____
<b>As a passenger in a car for an hour without a break</b>	_____
<b>Lying down to rest in the afternoon when circumstances permit</b>	_____
<b>Sitting and talking to someone</b>	_____
<b>Sitting quietly after a lunch without alcohol</b>	_____
<b>In a car, while stopped for a few minutes in traffic</b>	_____

**Total Score** \_\_\_\_\_

**Epworth Sleepiness Score. Jones MW A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991 14:540-5**

**This part is to be completed after completion of the 2<sup>nd</sup> period only (end of study)**

Comparing the 2 modes of ventilation together, please answer the following questions:

**A. Regarding ease and comfort of breathing on the ventilator, which mode was more comfortable? Circle the most appropriate answer**

**1- Mode A (first 2 weeks)                      2- Mode B (second 2 weeks)**

**B. Regarding level of energy during daytime, on which mode did you feel better? Circle the most appropriate answer**

**1- Mode A (first 2 weeks)                      2- Mode B (second 2 weeks)**

**C. Regarding feeling fresh in the morning, on which mode did you feel better? Circle the most appropriate answer**

**1- Mode A (first 2 weeks)                      2- Mode B (second 2 weeks)**

**D. Regarding morning headaches, which mode was less associated with headaches? Circle the most appropriate answer**

**1- Mode A (first 2 weeks)                      2- Mode B (second 2 weeks)**

**E. Regarding quality of sleep, on which mode did you feel better? Circle the most appropriate answer**

**1- Mode A (first 2 weeks)**

**2- Mode B (second 2 weeks)**

### Appendix 3: Study protocol

1. Following enrolment and randomisation, the patient will be allocated either treatment A (e.g. Spontaneous - S) or B (e.g. Spontaneous Timed – ST) according to the setting in the sealed envelope (Refer to step 7).
2. The ventilator used will be a “Resmed VPAP III ST-A”.
3. The participants will attend the sleep laboratory on one afternoon (2 pm) and overnight where baseline data (patient demographics) & measurements (height, weight) will be collected and the machine settings determined for both arms of the study. This initial study will also ensure that the ventilator settings are safe for the patients.
4. If the patient is on a pressure-cycled ventilator, the same amount of pressure support as their original setting should be set for the (S) and (ST) mode.
5. To set the respiratory rate for ST mode, count the respiratory rate for the patient on the prescribed pressure support at rest and set the rate accordingly.
6. If the patient is originally on a volume-cycled mode, set the EPAP at 4-6 cm H<sub>2</sub>O, and the IPAP at a value that achieves a comfortable or similar tidal volume (TV) to his/her original setting (roughly 10ml/kg). Ensure the patient is happy with this completely new setting.
7. The patient then will have a sleep study with all the usual parameters for a VRSS patient on the spontaneous mode. If adjustments to the ventilation settings are needed, this will be done by the unblinded staff member.
8. Once the appropriate settings are set, the unblinded staff member will allocate the participant to one of the arms, according to a computer-generated program. The allocation will be sealed in an envelope with the patient’s number on it (e.g. Patient 1, patient 2 ...etc). The patient will be blinded to the mode of ventilation allocated.
9. Patients, who require a change of mask, will be fitted as needed at the start of the study.
10. The patient will then be discharged home on the allocated setting for a period of two weeks.
11. The patient will then return back to the sleep laboratory to have a sleep study to collect the data for this mode.
12. Arterial blood gases will be obtained in the evening prior to initiation of ventilation and in the morning post ventilation in a seated position.
13. Other data include oxygen and carbon dioxide levels, number of arousals, the apnoea hypopnea index, quality of sleep, the presence or absence of leak and triggering problems.
14. The scientist scoring the study will be blinded to the mode of ventilation allocated and so are the researchers who assess the study and collect the data.
15. The patient will also be asked to fill out a questionnaire regarding overall comfort on the ventilator, sleep quality and daytime activity.
16. The principal researcher will perform a PVT after the questionnaire.
17. If possible download data from the machine for that night.
18. The participant will then be discharged home for a washout period of 2 weeks.
19. After this he/she will be allocated the second mode of ventilation by the unblinded staff member and the ventilator sent to the patient’s home address.
20. The patient will then return back to the sleep laboratory to have a 3<sup>rd</sup> sleep study to collect the data for this mode. Arterial blood gases and other data will be collected as above.
21. Before discharge home the patient will fill out the 2<sup>nd</sup> and final questionnaire and perform the second PVT.
22. If the patient needs another change of mask for his original mode of ventilation, this should be done also prior to discharge.

## Appendix 4:

### Troubleshooting/ Safety sheet for Restrictive Lung Disease Study

#### 1- Rise in CO<sub>2</sub> during sleep study:

If there is a progressive rise in PtcCO<sub>2</sub> more than 10 mmHg or the absolute PtcCO<sub>2</sub> is > 60 mmHg

- Ensure a good mask fit etc
- Ensure the patient is triggering properly
- Check tidal volume
- If above is adequate → increase the pressure support (IPAP) by increments of 2 as required as per protocol (please do not alter RR)

#### 2- Desaturation:

For desaturation < 88% or 5% less than baseline →

- check for adequate ventilation as above (leak, pressure support, triggering etc ...)
- If obvious obstructive events → increase EPAP (as usual)
- If the patient is on oxygen (unlikely) → make sure it is connected and implemented properly

#### 3- Intolerance of treatment:

- Troubleshoot as per item 2
- If no significant abnormality, but the patient is not used to the new mode → try to encourage the patient to continue if possible until we review the study in the morning.
- If there is a clear failure of treatment (see below for definition) or the participant refuses to continue with the new mode → the patient can go back on their usual mode of ventilation

#### Treatment failure:

- Persistent rise in PtcCO<sub>2</sub> of more than 10 mmHg or an absolute PtcCO<sub>2</sub> is > 60 mmHg despite efforts to troubleshoot as above
- Persistent desaturation < 85% > 50% of the time during the study despite troubleshooting as above
- The patient is unable to tolerate the mode of ventilation
- Staff are concerned for other reasons that imply the treatment mode is not safe
- The patient is admitted to hospital with respiratory failure

## Appendix 5: Exploratory statistics

### 5.1 Friedman's ANOVA for Ineffective efforts

There was a statistically significant difference between mean rank of Spontaneous Mode (S) and Spontaneous Timed Mode (ST) with values of 1.9 and 1.1 respectively (P 0.046) as per table.

#### Ranks

	Mean Rank
Unrewarded efforts A	1.90
Unrewarded efforts B	1.10

#### Test Statistics<sup>a</sup>

N	5
Chi-Square	4.000
df	1
Asymp. Sig.	.046

Table A.13: Friedman's ANOVA for Ineffective efforts

### 5.2 Friedman's ANOVA for Poor triggering

#### Ranks

	Mean Rank
POOR TRIGGERING (hr:min:sec)	1.70
POORTRIGGERINGhrminsec_B	1.30

#### Test Statistics<sup>a</sup>

N	5
Chi-Square	2.000
df	1
Asymp. Sig.	.157

Table A.14: Friedman's ANOVA for poor triggering

