The University Of Sheffield.

MECHANICALLY ASSISTED COUGH IN MOTOR NEURONE DISEASE

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Abstract:

Motor Neurone Disease (MND) is a disabling and inevitably fatal disease, usually with a life expectancy of 2-3 years from symptom onset. It is characterised by progressive wasting and weakness in bulbar, limb and respiratory muscles. There is no cure and treatment is mainly symptomatic. Neuromuscular respiratory failure, with or without a chest infection, is the commonest cause of death in MND patients. It has been shown that supporting respiratory function with non-invasive ventilation, improves survival and quality of life despite progression of the disease. The patients with respiratory muscle weakness may also have a weak cough and significant difficulty in clearing their airways of respiratory secretions. This causes much discomfort, predisposes to chest infections and adversely affects quality of life. Due to lack of evidence in this area, there is no clear consensus or guideline about how best to help such patients. This work aimed to establish the role of cough augmentation techniques in MND.

A total of 40 eligible patients with MND were randomised to the breath-stacking technique (n=21) or Mechanical Insufflator-Exsufflator MI-E (n=19) and followed-up at 3 monthly intervals for at least 12 months or until death. All patients were diagnosed with respiratory failure and offered non-invasive ventilation (NIV). The primary outcome measure was the number of days with symptoms of chest infection, treated with antibiotics, in the community or in hospital. Survival and quality of life benefit, assessed by short form 36 mental component summary (MCS) and sleep apnoea quality of life index symptoms domain (sym), were the secondary outcome measures.

There were 13 episodes of chest infection in the breath-stacking group and 19 episodes in MI-E group (p=0.87), requiring 90 and 95 days of antibiotics respectively (p=0.85). There were 6 episodes of hospitalisation in each group (p=0.87). The mean duration of symptoms per chest infection was 6.9 days in the breath-stacking group and 3.9 days in MI-E group (p=0.16). The chance of hospitalization, in the event of a chest infection was 0.46 in the breath-stacking group and 0.31 in MI-E group (p=0.47). Median survival in the breath-stacking group was 535 days and 266 days in the MI-E group. The MCS score was maintained above 75% of baseline for a median of 329 days in the breath-stacking group and 205 days in MI-E group (p=0.41). A

non-significant improvement in quality of life, compared to baseline was observed in both interventional groups.

In MND patients with respiratory failure, cough augmentation is likely to help maintain quality of life in the presence of the distressing symptom of weakened ability to cough. This study was not powered to assess the potential impact on life expectancy. There was no significant difference in terms of pulmonary morbidity between the two groups. A trend towards fewer chest infections was observed in the breath-stacking group, and a trend for reduced duration of antibiotic use and decreased chance of hospitalization in the event of a chest infection was observed in the MI-E group, though these changes did not reach statistical significance. These results are insufficient to draw firm conclusions, but support routine domiciliary use of a suitable cough augmentation technique in patients with ALS requiring respiratory support. The breath-stacking technique may be prescribed for domiciliary use with the onset of respiratory failure. MI-E may be useful in the event of a chest infection when it has the potential to reduce the duration of antibiotic use and chance of hospitalisation or when breath-stacking is no longer sufficient to maintain patient comfort. The results of this trial provide data useful for the power calculations required for a larger-scale multi-centre randomised trial.

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ABBREVIATIONS

ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale – revised
BiPAP	Bilevel positive airway pressure
BMI	Body mass index
CHMP2B	Charged Multi vesicular body protein 2B
CNS	Central Nervous System
COX	Cyclo-oxygenase
CO_2	Carbon dioxide
CMAP	Compound motor action potential
CPT	Chest Physiotherapy
CSI	Caregiver Strain Index
CSF	Cerebrospinal fluid
Cu/Zn	Copper/Zinc
DNA	Deoxyribonucleic Acid
EAAT	Excitatory Amino Acid Transporter
EMG	Electromyography
ERV	Expiratory reserve volume
FET	Forced Expiratory technique
FEV_1	Forced expiratory volume in one second
FRC	Functional residual capacity
FUS	Fused in sarcoma

FVC	Forced Vital Capacity
H^+	Hydrogen ion
HFCWO	High Frequency Chest wall Oscillation
IRV	Inspiratory reserve volume
kPa	kilo Pascal (unit of pressure)
LMN	Lower motor neurone
LVR	Lung volume recruiter
MAC	Manually assisted coughing
MCP	Monocyte Chemotactic Protein
MCS	Mental component summary
MIC	Maximal insufflation capacity
mmHg	Millimetre of mercury (unit of pressure)
MND	Motor Neurone Disease
MI-E	Mechanical In-Exsufflator
MIC	Maximum Insufflation Capacity
MRI	Magnetic resonance imaging
NHS	National Health Service
NIV	Non-Invasive Ventilation
NREM	Non-rapid eye movement
PBP	Progressive Bulbar Palsy
Pcbg	Capillary pressure
PCF	Peak Cough flow

Pdi	Diaphragmatic pressure
pH	Power of hydrogen ion
Poes	Oesophageal pressure
PLS	Primary Lateral Sclerosis
PMA	Progressive Muscular Atrophy
$PtcCO_2$	Transcutaneous partial pressure of carbon dioxide
QoL	Quality of Life
REM	Rapid eye movement
RNA	Ribonucleic acid
RV	Residual volume
ScHARR	School for health and related research
SpO_2	Oxygen Saturation
SAQLI sym	Sleep Apnoea Quality of Life Index symptoms domain
SF-36	Short Form – 36
SITraN	Sheffield Institute for Translational Neuroscience
SNIP	Sniff nasal inspiratory pressure
SOD	Superoxide Dismutase
SVC	Slow vital capacity
TAR	Transactive response
TDP	TAR DNA Binding protein
TwPdi	Twitch transdiaphragmatic pressure
TwPmo	Twitch mouth pressure

TLC	Total lung capacity
TNF	Tumour necrosis Factor
TOSCA	Transcutaneous carbon dioxide monitor (brand name)
TV	Tracheostomy ventilation
TV	Tidal volume
UK	United Kingdom
UMS	Unilateral magnetic stimulation
UMN	Upper motor neurone
VC	Vital Capacity
VEGF	Vascular Endothelial Growth Factor

CHAPTER 1

INTRODUCTION

Section 1:

Motor Neurone Disease

1.1) Definition and epidemiology

Motor neurone disease (MND) is a devastating neurodegenerative condition, characterised by progressive loss of motor neurones in the nervous system. It is the 3rd commonest neurodegenerative disease, after Alzheimer's disease and Parkinson's disease. The annual incidence is 2 per 100,000; high mortality leaves a prevalence of 5-7 individuals per 100,000 population[1,2]. The mean age of onset is approximately 55-60 years although it may affect adults of all ages, with a slight male predominance (1.6:1). The prevalence of MND is uniform in most parts of the world. In the UK 1,200 new cases are diagnosed each year. It has been estimated by the Motor Neurone Disease Association, UK that there are about 5000 individuals living with MND in the UK and five patients die every day of this condition[3,4].

1.2) Clinical presentation

The presentation of motor neurone disease is variable and depending on the region of the nervous system affected, the disease may have limb (commonest), bulbar, respiratory or mixed onset. The usual presentation is with speech and swallowing problems; cramps, twitching, or weakness and wasting in the limb muscles; loss of manual dexterity, foot drop or unprovoked falls. Rarely, symptoms of respiratory failure such as shortness of breath, orthopnoea, sleep disturbances etc. are the presenting feature of MND. In the later stages of the disease most patients have clinical evidence of degeneration of both upper and lower motor neurones in the bulbar region and at least two other spinal regions. This gives rise to the most common phenotype of MND - Amyotrophic Lateral Sclerosis (ALS – 70% of the cases) and hence the term ALS is considered synonymous with MND in certain parts of the world. Other clinical subtypes of MND include *Primary Lateral Sclerosis* (PLS – 2% of cases) which predominantly affects upper motor neurones, *Progressive Bulbar Palsy* (PBP – 20% of cases) which predominantly affects bulbar motor nuclei and their supranuclear connections and *Progressive muscular atrophy* (PMA – 10% of cases) which predominantly affects lower motor neurones. Flail arm and flail leg syndrome are also considered MND variants as they share the same molecular and cellular pathology[3]. Bulbar onset is more common in women and in elderly patients, with 43% of those above 70 presenting with bulbar symptoms[5]. Traditionally described as a disorder of motor neurones, MND is now being recognised as a multi-system disorder. Extra-motor regions of the CNS affected by the pathological process include

frontotemporal cortex, hippocampus, thalamus, substantia nigra, spinocerebellar and sensory pathways. Interestingly extra-ocular and pelvic muscles are spared or affected late in MND. Fronto-temporal dementia occurs in approximately 5% of MND cases but more subtle cognitive dysfunction may be seen on neuropsychology testing in up to 30-50% of patients[6]. The rate of progression of motor neurone disease is variable but average life expectancy is 2-3 years from symptom onset. About 10% of the patients live longer than 10 years.

1.3) Pathology

The pathological hallmark of MND is the degeneration of both upper and lower motor neurones in the brain and spinal cord which is reflected macroscopically as atrophy of the cerebral precentral gyrus; pallor, shrinkage and sclerosis of the corticospinal tracts and pallor of the anterior horns of the spinal cord at the affected segments. The neuronal loss in the central nervous system is associated with astrocytic gliosis. Loss of upper motor neurones causes spasticity and hyperreflexia in the affected muscles while loss of lower motor neurones causes weakness and wasting of the respective denervated muscles.

Microscopic features of the degenerating motor neurones include Bunina bodies and ubiquitinated proteinaceous inclusions within motor neurone cell bodies and accumulations of neurofilament within motor neurone axons[7]. The TAR-DNA binding protein of 43 KDa (TDP-43) has recently been identified as a major component protein of the ubiquitinated inclusions in MND[8], except in patients with SOD1 mutations. Muscles affected by MND show clusters of atrophic angular fibres (reflecting denervation) and collateral sprouting of intramuscular axons (reflecting re-innervation).

1.4) Aetiology and risk factors

A number of environmental and genetic risk factors have been proposed in the pathogenesis of MND.

1.4.1) Genetic risk factors

MND is more commonly a sporadic disease, 5-10% of the cases have a family history. At least 12 different gene mutations have been identified in the families affected with MND (Table 1). The most recent discovery is the identification of intronic hexanucleotide expansion in the C9ORF72 gene (on chromosome 9p), which is responsible for up to 40% of familial cases and 7-8% of sporadic cases[9,10]. The exact disease mechanism associated with C9ORF72 is unknown, abnormal C9ORF72 transcription and generation of toxic RNA foci have been postulated. Mutations in the SOD-1 gene (on chromosome 21q) encoding the free radical scavenging enzyme copper-zinc superoxide dismutase 1 accounts for approximately 20% of familial cases[11].

The most common form of inheritance is autosomal dominant, although autosomal recessive and X-linked inheritance may also be seen in some pedigrees. The pathways that lead to the neuronal death in the presence of mutant SOD1 are complex and currently not fully delineated (see section 1.5). SOD1 is also widely expressed in all other tissues of the body and it is not fully understood why motor neurones are especially vulnerable to injury in the presence of SOD1 mutations. About 2-5% of familial MND have mutations in the TDP-43 gene (encoding TAR-DNA binding protein 43)[12]. These mutations are also rarely seen in apparently sporadic cases[13]. Eight additional gene mutations (*ASL2* - *ALS8*) have been identified as causative in rare cases of familial MND. Several "susceptibility" gene mutations have been identified in sporadic cases which may act as genetic risk factors for developing the disease, when exposed to certain environmental/life style risk factors. These include alterations in the vascular endothelial growth factor (*VEGF*) gene, haemochromatosis gene (*HFE*), ataxin-2, angiogenin, dynactin, neurofilament heavy chain, peripherin, progranulin, apolipoprotein E and *CHMP2B*, to name a few[14].

Table 1 Most common genetic causes of familial MND

Gene mutation	frequency	Proposed pathogenic mechanism	Evidence
Hexanucleotide repeat expansion in gene C9ORF72	40% of familial cases	unknown	(DeJesus-Hernandez et al.)
Mutations in SOD1 gene	20% of familial cases	Not fully understood, evidence for toxic gain of function[15]	(Rosen et al.)
Mutations in TDP-43 gene	5% of familial cases	Role in RNA metabolism	(Sreedharan et al.)
Mutations in FUS gene	4-5% of familial cases	Role in RNA metabolism	(Vance et al.)

1.4.2) Environmental risk factors

There has been great interest in identifying the environmental risk factors, as avoiding them could prevent or delay the development of this serious disease.

A much higher incidence of MND was observed in Western Pacific sites (Guam and the Kii Peninsula of Japan) where the prevalence was much higher during 1950-1954 but then steadily declined. Dietary constituents of the native Chamorro people which contained a glutamate like excitotoxin have been suspected as a potential risk factor[16]. Another cluster was reported in the Persian Gulf War veterans. Military service has also been postulated as a potential risk factor and physiological and psychological stress are possible explanations for this higher incidence[17]. Other environmental neurotoxicants such as heavy metals, solvents and pesticides and occupational exposure to these have been suspected in the aetiology of MND[18]. Putative life style risk factors include extreme physical activity (which may be occupational or recreational)[19], physical trauma (including electric shock)[20], cigarette smoking[21] and high dietary fat intake[22]. However, many of the reported epidemiology studies are under powered, have poorly matched control groups and the results are often inconsistent and conflicting. Only smoking has been proven as a significant risk factor through an evidence based approach. Male sex is an independent risk factor, a slightly higher incidence is observed in men (1.6:1). Better designed large population based epidemiological studies are needed to ascertain the environmental risk factors for MND.

1.5) Pathogenesis

The precise mechanism underlying selective cell death in motor neurone disease is currently unknown. Current understanding is that cell death is likely to be the end point of multiple pathogenic processes (Figure 1)[23]. They may not be mutually exclusive and their cumulative effect may cause death of motor neurones. The following mechanisms have been put forward:

- **Oxidative stress:** Neurones are non-replicating, terminally differentiated cells and oxidative damage accumulated during life years may cause deterioration in neuronal function and a decline in number with advancing age. The SOD 1 gene mutations as an established cause of familial MND and evidence of abnormal free radical metabolism in

patients with MND supports the concept that oxidative stress contributes to motor neurone injury in MND. Post-mortem studies on CNS tissue from patients with MND have shown evidence of damage caused by abnormal free radical metabolism which was more pronounced than in the controls[24]. Similarly, fibroblasts cultured from the skin of patients with MND show more sensitivity to oxidative challenge than fibroblasts from controls[25]. The presence of mutant TDP-43 protein also induced oxidative stress in an *in vitro* motor neurone model[26]. Oxidative damage to mitochondrial proteins and lipids may be responsible for mitochondrial dysfunction in patients with MND. Anti-oxidants such as vitamin C and E are commonly prescribed to the MND patients, although evidence from well-designed clinical trials is lacking[27].

- **Mitochondrial damage and dysfunction:** Mitochondria have important roles in energy production, calcium homeostasis, ageing and apoptosis. There is a wealth of evidence supporting the role of mitochondrial dysfunction in the pathogenesis of MND[28]. Observations in this context include abnormal mitochondrial morphology and increased mitochondrial volume and calcium levels within motor axon terminals in sporadic MND[29]. Also, reduced activity of complex IV of the mitochondrial respiratory chain is reported in sporadic MND[30]. Moreover, mitochondrial DNA mutations have been identified in MND patients[31].

- **High metabolic activity:** Motor neurones are large cells having high energy demands and thus a high level of mitochondrial activity and also a high level of Cu/Zn superoxide dismutase activity to combat with free radicals generated during the energy combustion process. Impaired energy production affects axonal transport, intracellular calcium homeostasis and mitochondrial function. This may explain the relatively selective vulnerability of motor neurones to degeneration in the face of SOD1 mutation and mitochondrial dysfunction.

- **Excitotoxicity:** Glutamate is the major excitatory neurotransmitter in the human CNS. One theory suggests that function of the major glial glutamate reuptake transporter protein, excitatory amino acid transporter 2 (EAAT2) may be impaired in the CNS of patients with MND[32]. Overstimulation of post-synaptic glutamate receptors with excessive glutamate

results in premature death of neurones by deranging intracellular calcium homeostasis and production of free radicals. Glutamate levels have been found to be elevated in the CSF of patients with MND, though this is not a consistent finding[33]. This theory is supported by the fact that Riluzole (the only licensed treatment for slowing disease progression in MND), inhibits glutamate release at the nerve terminals[34].

- **Impaired axonal transport:** Neuronal axons have a transport mechanism (axoplasmic transport) which allows trafficking of cargos between the cell bodies and nerve terminals. Neurofilament proteins form the axonal cytoskeleton and motor proteins: kinesin and dynein transport cargoes in an anterograde and retrograde fashion respectively along microtubules within the axons. Axonal transport is essential for the growth and survival of neurones. Impaired axonal transport may cause an energy deficit in the distal axon and recent evidence suggests that the neuromuscular junction and distal axonal compartment are affected early in the disease pathology[35]. Deranged neurofilament proteins and their abnormal assembly are seen within degenerating motor neurons (axonal inclusions). Mutations in the genes coding for the transport proteins (e.g. dynactin) are also known to cause motor neurone disorders[36]. Mutation in the microtubule associated protein tau gene is reported in frontotemporal dementia-Parkinsonism complex and has been suspected as a susceptibility gene for the Guam variant of MND[37,38].

- **Apoptosis:** Apoptosis is genetically programmed cell death pathway, designed to remove unwanted cells without inducing an inflammatory cascade. It is regulated by a number of pro- and anti-apoptotic proteins. Significantly increased activity of caspases 1 and 3 (key pro-apoptotic proteins) has been reported in the spinal cord of symptomatic mutant SOD1 transgenic mice and deceased patients[39]. Over expression of Bcl-2, a protein that inhibits apoptosis has been shown to delay the onset of motor neurone disease in mouse models[40].

- **Inflammation:** Inflammatory cytokines such as Monocyte chemo attractant protein-1, Cycloxygenase-2, Tumour necrosis factor α and interleukins have been found to be elevated in CSF of patients with MND and hence an inflammatory process has been suggested in the pathogenesis of MND[41-43]. However, clinical trials evaluating the use of inflammatory modulators have not so far shown promising results.

- **Glial activation:** There are abundant microglia (macrophages of the CNS) in the pathologically affected parts of CNS and these cells may play a part in the pathogenesis of ALS[44]. Activated glial cells release pro-inflammatory cytokines which may cause damage to the motor neurones. Minocycline inhibits glial activation and has been shown to slow the disease process in mutant SOD1 mice. However, a US trial of Minocycline in ALS patients has been unsuccessful[45].

- **Role of non-neuronal supporting cells:** Astrocytes are the most abundant supporting cells in the CNS whose function is to maintain the internal milieu of the CNS. Dysfunction of astrocytes has been investigated in the pathogenesis of MND. Astrocytes may contribute to the excitotoxic damage to the motor neurones by down regulating the glutamate reuptake transporter EAAT2 or actively releasing the glutamate excitatory neurotransmitter. Also, reactive astrocytes secrete inflammatory mediators and release pro-apoptotic proteins which may trigger apoptosis in motor neurones.[46]

- **Defective RNA processing:** Mutation in the genes encoding for Fusion in Sarcoma (FUS) and TDP-43 are linked to familial MND. FUS and TDP-43 are involved in RNA processing pathways. Defect in RNA processing and defective interaction between specific RNAs and RNA binding proteins in the cytoplasm may result in degeneration of motor neurones[47,48].

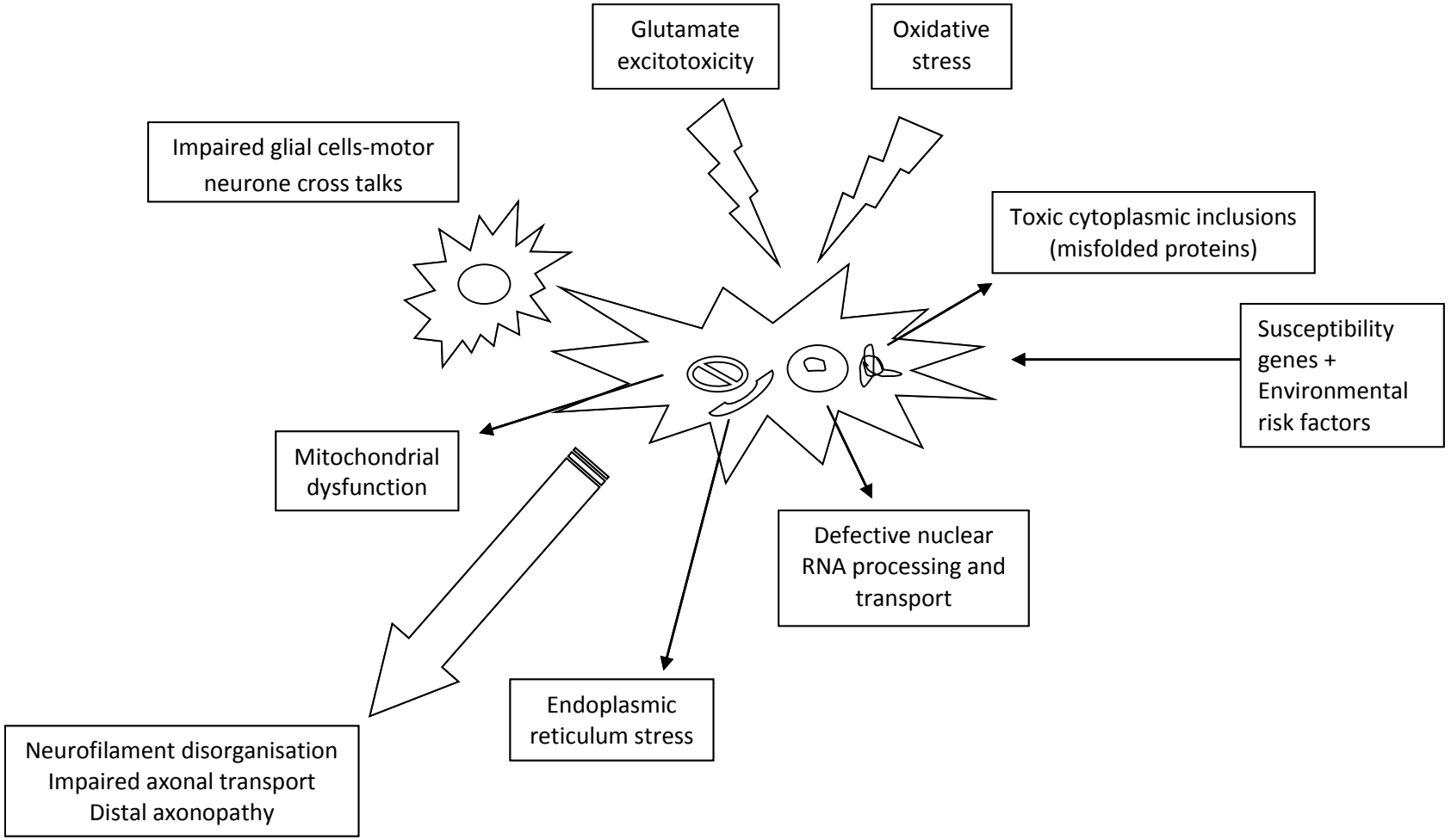


Figure 1: Suggested pathogenic mechanisms implicated in motor neurone degeneration

1.6) Diagnostic criteria

The diagnosis of MND is largely clinical and by exclusion. There is no diagnostic test or biomarker for MND. Patients with suspected MND generally undergo a range of investigations including serological tests, CSF studies, MRI scan (of the brain and spinal cord) and electromyography (EMG), along with genetic tests. It is important to rule out disorders which may mimic MND and may have a more favourable prognosis or are amenable to treatment e.g., pure motor neuropathies, inclusion body myositis, Kennedy's disease and multifocal motor neuropathy with conduction block. The EMG is the most useful test in confirming a clinical diagnosis of MND, while MRI of the respective spinal segments helps to rule out any structural lesion which may be causing the EMG changes.

A confident diagnosis of MND requires the presence of UMN and LMN signs at multiple spinal segments. El Escorial criteria for ALS (Table 2) has been developed through an international consensus and is used worldwide for research purposes to allow consistency. However, according to these criteria to make a "clinically definite" diagnosis the patient is required to have fairly advanced disease, when approximately 80% of motor neurones would have been lost. On initial presentation only UMN or LMN signs may be present and only come together during subsequent disease progression.

Table 2: Revised El Escorial Criteria for the diagnosis of ALS (1998)

- The diagnosis of **"Definite ALS**" is made solely on clinical grounds, with the presence of upper and lower motor neurone signs in the bulbar region and at least two other spinal regions (cervical, thoracic, lumbar) or with the presence of UMN and LMN signs in three spinal regions.
- The diagnosis of **"Probable ALS**" is made on clinical grounds only with the presence of upper and lower motor neurone signs in at least two regions. Moreover, some UMN signs must be rostral from the LMN signs.
- The diagnosis of **"Probable – Laboratory-supported ALS**" is made on a combination of clinical grounds by the presence of UMN and LMN signs in one region, or UMN in one region with neurophysiological evidence for LMN involvement in two regions. As with the above neuroimaging and other laboratory techniques should be used to exclude other diseases.
- The diagnosis of "**Possible ALS"** can be made with UMN and LMN signs in one region, not explained by any other pathology.
- The diagnosis of **"Suspected ALS"** is made with only LMN signs in one or more regions or only UMN signs in one or more regions.

1.7) Causes of morbidity and mortality

Major causes of morbidity and mortality in MND are described below.

1.7.1) Falls: Falls due to neuromuscular weakness are common, can be serious and contribute significantly towards the heath care cost of MND patients[49]. It may not only be associated with physical morbidity but also have emotional impact, adversely affecting the self-confidence of patients. In one large multi-centre clinical trial involving patients with MND, falls were the third commonest reported adverse events[45].

1.7.2) Respiratory failure: With the relentless progression of degeneration of the motor neurones supplying the respiratory muscles, hypoventilatory respiratory failure is an inevitable manifestation of advancing disease. Failure of the respiratory pump gives rise to a variety of symptoms which contribute significantly to the morbidity of patients with MND and cause eventual death from carbon dioxide narcosis. Respiratory failure is widely cited in the literature as the commonest cause of morbidity and mortality amongst patients with MND[50].

1.7.3) Aspiration and chest infections: MND may affect both upper and lower motor neurones controlling the tongue, palatal, pharyngeal and laryngeal muscles. Patients may gradually lose the ability to swallow and fail to close the glottis and thus lose the ability to protect their airways from aspiration of food and saliva. Even in those patients who have stopped eating orally, aspiration of saliva may cause recurrent chest infections. Moreover, the strength of cough reflex is impaired in most patients and physiological respiratory secretions may pool in the lungs where they may act as nidus of infection. Thus patients with MND are predisposed to chest infections which may precipitate acute or acute-on-chronic respiratory failure which is often life threatening.

1.7.4) Malnutrition: MND patients are particularly predisposed to malnutrition for a variety of reasons, which include dysphagia because of the involvement of bulbar muscles, fear of choking and aspiration, inability to feed themselves and high resting metabolic rate[51]. In an American survey of causes of hospitalization in MND, dehydration and malnutrition were the most common causes, accounting for 36% of hospital admissions[52]. Malnutrition during the course of disease is an independent prognostic factor for survival, with a fourfold increased

risk of death in patients with malnutrition[53]. Malnutrition contributes to morbidity by worsening neuromuscular weakness, reduced resistance to infections and causes depression, thus adversely affecting quality of life.

1.7.5) Psychological problems: Patients with MND experience a number of psychological stressors such as frustration due to inability to speak and express themselves, low self-esteem resulting from dependence on others, anxiety about the unpredictable course of disease and depression due to social isolation and poor quality of life. However, major depressive disorder is uncommon in patients with MND[54]. Emotional lability (exaggerated emotional reflexes) is a common symptom, especially in the bulbar form of MND. Psychological health has an impact on survival and quality of life of these individuals[55].

1.8) Treatment

MND is incurable and therapies which alter survival are limited. Riluzole (Rilutek®) is the only drug tested in a placebo controlled trial which has shown robust evidence of a survival benefit[56]. However, it improves survival by only 3-4 months when taken for a period of 18 months and this benefit is also dependent on factors like duration of symptoms, age and forced vital capacity (FVC)[57]. Multiple other medicinal products have been tested without encouraging results. Anti-oxidants (especially vitamin E) are commonly prescribed on theoretical grounds, though firm evidence of benefit from human trials is lacking. In the absence of a significant disease modifying drug, emphasis has been placed upon the management of symptoms to allow the patients have a good quality of life. In this regard supporting ventilation by non-invasive means and maintaining nutrition with enteral feeding have been the most significant advances.[58]

1.9) Prognostic factors

The prognostic factors at the time of diagnosis of MND are summarised in table 3.

Table 3: Prognostic factors at diagnosis

Parameter	Good prognostic factor	Poor prognostic factor
Age of onset[59]	Juvenile onset (< 55 yrs)	Late onset (> 55 yrs)
Gender[60]	Male	Female
Time from symptom onset and diagnosis[61]	> 1 year	< 1 year
Site of onset[62]	Limb onset	Bulbar onset
Form of Disease[59]	PLS/PMA/flail arm-leg	ALS/PBP
Respiratory function at diagnosis [63]	FVC > 75%	FVC < 75%
Weight [64]	Maintaining weight	Rapid weight loss
Bulbar function[60]	Mild to moderate bulbar impairment	Severe bulbar impairment
Mental health[65]	Positive attitude	Depression

* FVC – forced vital capacity, a measure of respiratory function

1.9.1) Indices of disease progression in MND

The following clinical parameters are used as markers of disease progression. They are used to inform prognosis and to plan supportive interventions. Rapid declines in these parameters indicate an aggressive disease and a worse prognosis.

- Weight loss
- Functional decline (commonly monitored with the revised ALS functional rating scale (ALSFRS-R))
- Declining muscle scores (evaluated by manual muscle testing)
- Decline in forced vital capacity (FVC) or other respiratory parameters

INTRODUCTION

Section 2:

Respiratory muscle weakness in Motor Neurone Disease

1.10) Skeletal muscles

Skeletal muscles are contractile tissues which contract in response to nervous stimulation and are generally under voluntary control. A skeletal muscle is made up of many individual muscle fibres, arranged in parallel, which generate a cumulative force of contraction. The muscle fibres contain myofibrils, which are divisible into individual filaments. These myofilaments contain the contractile protein myosin and the cytoskeletal protein actin, together they make up the contractile machinery of the skeletal muscle. The arrangement of myofibrils gives rise to characteristic cross-striations in skeletal muscles, when viewed under the microscope. Hence, skeletal muscles are often called striated muscles. In skeletal muscles, unlike cardiac and smooth muscles, each muscle fibre is functionally distinct and there are no syncytial bridges between individual muscle fibres[66].

The myofibrils are surrounded by a system of tubules, T tubules and sarcoplasmic reticulum. T tubules communicate with the extracellular space and provide a path for the rapid spread of the action potential from the cell membrane to all the myofibrils. The sarcoplasmic reticulum stores calcium which has an important role in muscle contraction. The action potential starts at the motor end plate (the specialized structure under the motor nerve terminal) and spreads along the muscle fibres, culminating in a contraction. The cycle of muscle contraction followed by relaxation is called a muscle twitch.

1.11) Anatomy of the respiratory system

The respiratory system consists of the airways (the conducting division), the lungs (gas exchanging organ) and the thoracic cage (a pump that ventilates the lungs). This system is controlled in a co-ordinated fashion by the higher centres in the brain.

1.11.1) The airways

The nose through to the larynx is often called the upper respiratory tract and the airways from the trachea through the lungs form the lower respiratory tract. The function of the upper airways is to warm and humidify the inspired air, while removing any airborne particles. The

gas exchange takes place at the respiratory bronchioles and alveolar sacs. The airway is protected from the pharyngeal contents by the epiglottis. At rest, the epiglottis is in a vertical position, leaving the airway open. However, during swallowing extrinsic muscles of the larynx pull the larynx upwards, towards the epiglottis and the tongue pushes the epiglottis downwards towards the larynx. The epiglottis thus closes the airway and the pharyngeal contents are directed into the oesophagus. It is impossible to breathe and swallow at the same time without choking[67].

Apart from acting as a conducting medium for air, the upper airway has an important role in voice production. The vocal cords in the larynx produce sound when air passes between them. The sound thus produced is transformed into words by the pharynx, tongue, oral cavity and lips.

1.11.2) The lungs and bronchial tree

Each lung has a branching system of airways called the bronchial tree. The airways divide 23 times between the trachea and the alveolar sacs. These multiple divisions greatly increase the total cross-sectional area of the airways, from 2.5 cm^2 in the trachea to 11,800 cm^2 in the alveoli[66]. Consequently, the velocity of air flow in the distal airways reduces to very low values, allowing sufficient time for gas exchange. Branches of the pulmonary artery closely follow the bronchial tree, finally becoming pulmonary capillaries which surround the alveoli. Alveoli surrounded by the pulmonary capillaries form the functional unit of the respiratory system. The lungs do not expand or shrink themselves or create the air flow. This work is done by the muscles of the thorax. The only muscle in the lungs is the smooth muscle within the walls of the bronchi and bronchioles. These muscles are innervated by the autonomic nervous system and adjust the diameter of the airway, affecting the speed of airflow.

1.11.3) The thoracic cage

The lungs are housed within the thoracic cage made of 12 pairs of ribs, the thoracic spine and the sternum. The intercostal muscles and the diaphragm form the non-bony part of the thoracic cage, allowing expansion of the chest. The inner surface of the cage is lined by a serous membrane, the parietal pleura which represents an extension of the visceral pleura,

lining the lungs. The pressure within the thoracic cage is sub-atmospheric which assists in inflation of the lungs. Changes in volume of the thoracic cage are brought about by the contraction of the thoraco-abdominal muscles.

1.11.4) The respiratory muscles

The respiratory muscles are the effector organs for breathing. The respiratory muscles are numerous and extend from the nose to the abdomen and in addition to pulmonary ventilation, they participate in many other functions. Hence, neuromuscular diseases can affect respiratory function at several levels.

The diaphragm is the main muscle of pulmonary ventilation, accounting for about two-thirds of the pulmonary airflow. The diaphragm is assisted by the internal and external intercostal muscles. Apart from these "chief muscles", there are "accessory muscles" of respiration which aid breathing especially during forced respiration. These include the sternocleidomastoids, the scalene muscles of the neck, pectoralis minor and major and serratus anterior of the chest. The rectus abdominis and other lumbar, abdominal, and even pelvic muscles assist in forced expiration by raising the pressure in the abdominal cavity.

The respiratory muscles, like other skeletal muscles, have a servo-mechanism mediated by muscle spindles which control their tension. The diaphragm is composed of three types of muscle fibres i.e. highly oxidative, slow twitch or type 1 fibres; mixed oxidative-glycolytic, fast twitch or type 2a fibres; and glycolytic, fast twitch or type 2b fibres. There are about 55% type 1 fibres, 20% type 2a fibres, and 25% type 2b fibres in adult human diaphragm[68]. This distribution of fibre types is affected by nutritional status, training, and disease[69].

The force of contraction of a muscle is determined by the initial length of the muscle, the rate at which muscle is stimulated, and the velocity of shortening. The velocity of shortening of skeletal muscle depends on the composition of its fibre types and the activity of the adenosine triphosphatase (ATPase) of the myosin contractile element.

1.11.5) How respiratory muscles are different from other skeletal muscles

The respiratory muscles are different from typical skeletal muscles in a number of ways:

1. Respiratory muscles are semi-automatic i.e., normal automatic breathing can be modified voluntarily.
2. Respiratory muscles are fatigue resistant and may only develop fatigue during exhaustive exercise or in certain disease conditions.
3. Normally muscle function is assessed by comparing motor nerve input to the muscle with the force generated in the muscle during contraction. However, this principle is not fully applicable to respiratory muscles. The geometry of respiratory muscles changes in different body postures; this means that different forces will be generated by a given muscle for the same neural input in different body postures. Also, respiratory movements vary in different body postures despite similar neural input due to the passive influence of gravity.
4. Unlike other skeletal muscles, the force generated by respiratory muscles cannot be assessed directly and is measured in terms of respiratory pressures. These pressures are affected by the passive properties of the lungs and the rib cage.

1.12) Respiratory physiology

Respiratory physiology is complex and there is no single mechanism which can be considered to control ventilation. Resting ventilation (eupnea) is largely carried out by rhythmic contraction and relaxation of inspiratory muscles, while the rhythm is generated in the respiratory centres located in the brain stem. This "automatic breathing" can be overridden by voluntary cortical control. Many other mechanisms can also interrupt involuntary breathing such as coughing or sneezing, acts of micturition and defecation, breath holding (apneusis) and during exercise. Apart from gas exchange, another important function subserved by respiration is to control the internal milieu. Hence, blood biochemistry can influence the respiratory centres.

1.12.1) The origin of the respiratory rhythm

The actual site of origin of the automatic respiratory rhythm is disputed. The main respiratory centre is in the floor of the 4th ventricle, with inspiratory (dorsal) and expiratory (ventral) neurone groups. The inspiratory and expiratory neurones are linked by mutually inhibitory pathways, so that when one group of neurones is active, the activity dies away in the other group. Impulses from these neurones, via the reticulospinal tract, activate motor neurones in the cervical and thoracic spinal cord, which innervate respiratory muscles. The expiratory neurones influence the activity of expiratory muscles only during forced expiration and under resting conditions their role is to provide negative feedback to inspiratory neurones. In eupnoea, alternating neural activity between inspiratory and expiratory neurones produces a respiratory rhythm of about 12 cycles per minute. Wang *et al.* demonstrated that eupnoea was possible with an isolated medulla[70].

The two other main centres, located in the pons are the apneustic centre, which enhances inspiration, and the pneumotaxic centre, which terminates inspiration by inhibition of the inspiratory neurone group and apneustic centre through a negative feedback mechanism (Figure 2). The pontine respiratory centres receive input from the hypothalamus, limbic system and cerebral cortex and feed back to the medullary neurones. The apneustic and pneumotaxic centres having received input from several other centres of the nervous system, adapt breathing to special circumstances such as sleep, vocalisation and emotional responses

(e.g., anxiety, crying or laughing). The inspiratory neurones and the apneustic centre also receive input from the chemoreceptors and stretch receptors in the lungs through the vagal afferents. These impulses inhibit inspiratory discharge. When the pneumotaxic area is damaged, respiration becomes slower with increased tidal volume. Damage to the main respiratory centre causes loss of automatic breathing (Ondine's curse). The final integration of respiratory stimuli occurs at the anterior horn cells[71]. Breathing effort would cease if the nervous input to the thoracic muscles is severed or if the spinal cord is damaged high in the cervical region (above the origin of the phrenic nerves). The quantity of gas exchanged is related to metabolic needs, which vary with rest, activity and sleep. The respiratory muscles adjust their activity to meet these variable needs.

1.12.2) Chemical control of breathing

The respiratory centres in the brain stem are regulated by changes in arterial blood gases (Oxygen Po_2, and carbon dioxide Pco_2) and pH. The chemoreceptors that regulate respiration are located both centrally and peripherally.

- Central chemoreceptors are located in the medulla oblongata and are separate from the dorsal and ventral group of respiratory neurones. They respond to changes in the pH of the cerebrospinal fluid (CSF), which in turn reflects the CO_2 levels in the blood. CO_2 readily diffuses through the blood brain barrier and increases hydrogen ion (H^+) concentration in the CSF. Any rise in CSF H^+ concentration stimulates respiration, the magnitude of which is proportional to the rise in H^+ concentration. The response is sensitive to minor changes in Pco_2. Hence a stable pH and a stable CO_2 level in the blood are ensured.

- Peripheral chemoreceptors are the carotid and aortic bodies located in the respective great arteries. The receptors in the aortic and carotid bodies are stimulated by a rise in the PCO_2 or H^+ concentration or a decline in PO_2 of the arterial blood. Afferents from the aortic and carotid bodies exert influence on the respiratory centres via the vagi and the glossopharyngeal nerves respectively. The degree of hypoxia required to produce significant activation of the peripheral chemoreceptors is such that they are not influential under normal circumstances, but become activated if profound hypoxia (<8 kPa or 60 mmHg) occurs. With denervation of aortic and carotid bodies (e.g., as an accident of

neurosurgery), there is little change in resting ventilation, but the ventilatory response to a drop in PO_2 is abolished and the response to changes in arterial PCO_2 is reduced by 30%.

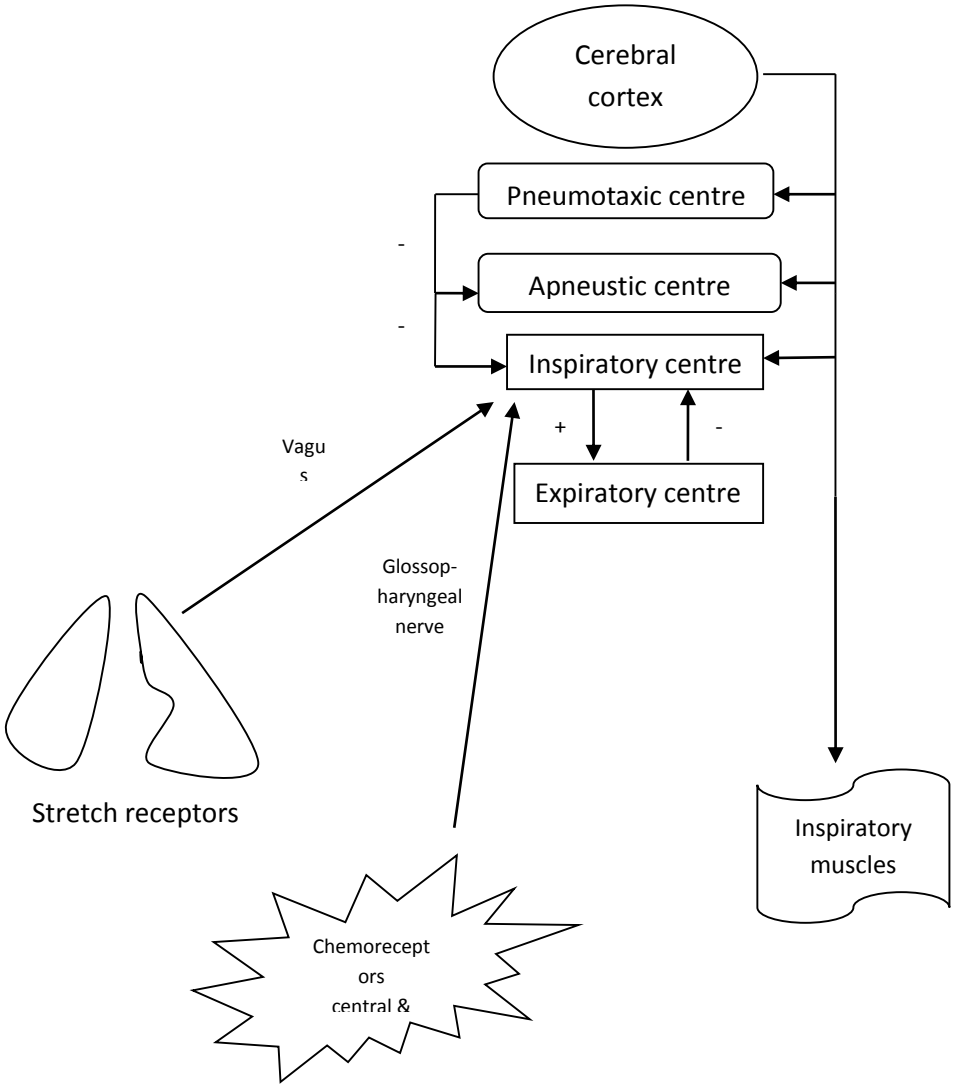


Figure 2: Central and peripheral control of breathing

1.12.3) Non-chemical influences on breathing

Stretch receptors are located in the smooth muscles of the airways and in the visceral pleura. They are activated in response to the inflation of the lungs and feedback to the inspiratory neurone group by way of the vagi. The depth of inspiration is increased after vagotomy due to lack of feedback from the pulmonary stretch receptors[67].

Irritant receptors are formed by the terminals of the unmyelinated C fibres scattered amid the airway epithelium. They respond to dust, smoke, pollen, cold air, chemical fumes and excess mucus. They transmit signals through the vagi to the respiratory centres, which in turn signal to the respiratory and bronchial muscles resulting in the production of protective reflexes such as coughing and sneezing.

1.12.4) Voluntary control of breathing

Automatic breathing can be controlled voluntarily for a brief period of time. It is important for functions such as singing, blowing, sniffing, speaking, breath holding, valsalva manoeuvre etc. The voluntary control originates in the motor cortex of the frontal lobe and sends impulses via the corticospinal tract to the respiratory motor neurones. Degeneration of the corticopinal tract impairs volitional control of breathing. This is frequently seen in patients with MND.

1.12.5) Effects of sleep on breathing

Sleep has four distinct stages without rapid eye movements (non-rapid eye movement, NREM) and sleep with rapid eye movement (REM). REM sleep is further subdivided into tonic and phasic REM sleep, depending on the presence or absence of intermittent short bursts of rapid eye movements.

Breathing continues during sleep, however with decreased tidal volume and minute ventilation[72] compared to when the subject is awake. The central respiratory drive is less than during wakefulness. Respiratory chemosensitivity to changes in both PCO_2 and PO_2 is reduced in sleep compared to wakefulness[73]. The PCO_2 is 3-5 mmHg higher during sleep than while wakeful. In healthy individuals lung volumes decrease only slightly during sleep.

Sleep adversely affects respiratory muscle strength and endurance. There is a decrease in skeletal muscle tone with sleep onset. During REM sleep, descending inhibitory activity originates in the pons and is most strongly expressed in the muscles with postural roles, such as the intercostals, neck and abdominal muscles. REM-induced loss of muscle tone affects the diaphragm to a lesser extent than other accessory muscles of respiration. Hence, during REM sleep the diaphragm generates the majority of the tidal volume[74]. During NREM sleep, the diaphragm is less active and intercostal muscle activity accounts for 60% of the tidal volume in NREM sleep. In normal subjects this has very little impact on ventilation. However, in neuromuscular disorders with a weak diaphragm, this leads to hypoventilation during REM sleep. The patients who have paralysis confined to the diaphragm manage to maintain adequate ventilation during NREM sleep as the intercostals, abdominal muscles and other accessory muscles maintain effective ventilation. One study showed reduced or absent REM sleep in patients with severe diaphragmatic dysfunction, which may reflect an adaptation[75]. Knowledge about the role played by sleep in the pathophysiology of respiratory failure in neuromuscular disorders has led to introduction of non-invasive ventilation to support breathing during sleep.

The relative contribution of the rib cage and abdomen to tidal volume is also affected by the supine posture. In the supine posture, due to the action of gravity on the abdominal contents, there is a reduced anteroposterior diameter of the abdomen at resting end-expiratory lung volume. Also, the pressure of the abdominal contents displaces the diaphragm upwards resulting in larger lateral and anteroposterior diameters of the rib cage at end-expiratory lung volume. The less distended abdominal wall is more compliant than the relatively more distended thorax. As a result, contraction of the diaphragm displaces the abdominal wall outward more than the chest wall and hence the movements of the chest wall is reduced during sleep. The majority of the volume displacement of the lung is reflected in abdominal movements[76]. In some instances there may be a paradoxical inward movement of the chest wall during inspiration in REM sleep. In the upright posture, the tidal volume displacement of the thorax is relatively greater with the rib cage accounting for about 70% of the tidal volume. Sleeping in the lateral position also gives rise to important mechanical differences between the two sides of the chest.

The upper airway resistance increases during sleep as a result of hypotonia of the pharyngeal muscles. These changes are more likely to occur in the supine position. Moreover, slight change in ventilation/perfusion ratios of different lung regions occur as one assumes the supine position from the upright position.

1.13) Mechanics of breathing

Breathing is brought about by two functionally distinct layers of thoracic muscles: the external intercostals (inspiratory) and internal intercostals (expiratory). An analogous group of muscles are the diaphragm (inspiratory) and the abdominal muscles (expiratory). Both the thoracic and abdominal walls move outward during inspiration and return inward during expiration. This is true in the supine as well as in the upright posture. The intercostal muscles act directly on the rib cage, increasing the transverse diameter of the rib cage (bucket handle movement). The diaphragm, using the abdominal contents as a fulcrum, lifts and expands the anteroposterior and vertical diameters of the rib cage (Figure 3).

There is normally a slight vacuum between the two layers of pleura, with a negative intrapleural pressure (normally about - 4 mmHg). As intra-thoracic volume increases with inspiration, intrapleural pressure falls to about - 6 mmHg. Some of this pressure change is transferred to the pressure within the alveoli (intrapulmonary pressure), which drops to about - 3 mm Hg. This pressure gradient between the atmosphere and alveoli makes the air, flow into the lungs. When the inspiratory muscles stop contracting, intrapulmonary pressure becomes equal to atmospheric pressure, and inflow stops. Resting expiration is primarily a passive process, achieved by the elastic recoil of lungs and chest wall. Due to recoil forces, intrapulmonary pressure increases to about + 3 mmHg. Air thus flows down the pressure gradient, out of the lungs. In forced expiration, intrapulmonary pressure can be raised to as high as + 30 mmHg[67].

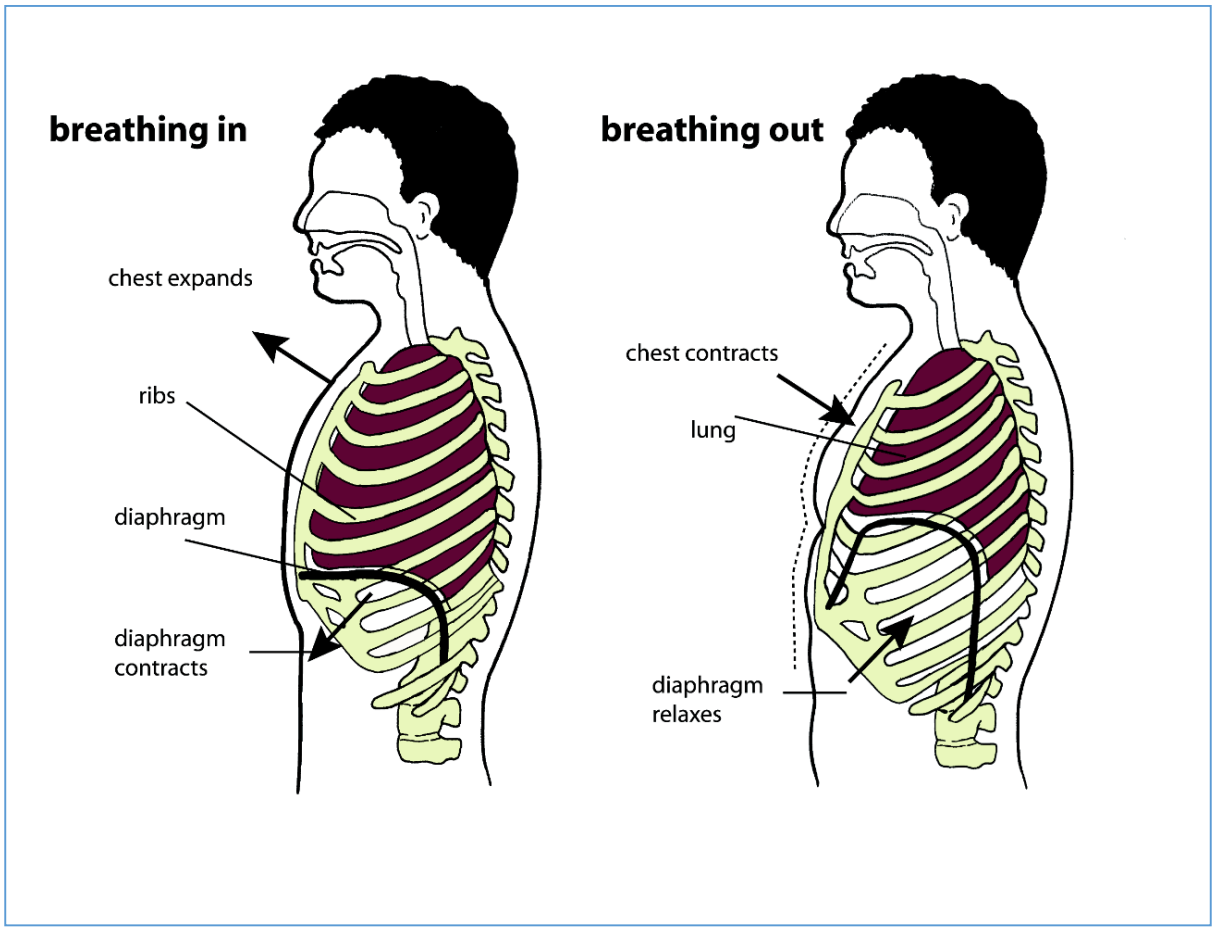


Figure 3: Mechanics of breathing

1.13.1) Work of breathing

Inspiratory muscles, to increase thoracic volume, have to generate pressure to overcome the resistance offered by the elastic tissues of the chest wall and lungs (approximately 65% of the work of breathing); inelastic tissues (viscous resistance - 7% of total work of breathing); and airways (airway resistance - 28% of total work of breathing)[77]. Diseases affecting any one of these may increase the work of breathing. When respiratory muscles cannot carry out the work of breathing, it leads to inadequate ventilation (pump failure).

1.13.2) Lung volumes

Lung volumes include Tidal volume (TV), which is the amount of air inhaled and exhaled in one cycle of quiet breathing. The normal value is about 500 ml. Inspiratory reserve volume (IRV) is the volume of air which can be inspired in excess of the TV with a maximal inspiratory effort, normally about 3000 ml. Similarly, expiratory reserve volume (ERV) is the volume of air which can be expired with a maximal expiratory effort beyond the amount normally exhaled. ERV is normally about 1200 ml. The amount of air left in the lungs after a maximal voluntary expiration is residual volume (RV), which is about 1200 ml. The amount of air left in the lungs at the end of quiet expiration is the functional residual capacity (FRC = ERV + RV). Total lung capacity is the sum of above volumes (IRV+TV+ERV+RV). The amount of air inhaled per minute is called respiratory minute volume, normally about 6 L (500ml/breath X 12 breaths/minute). Respiratory minute volume can be increased voluntarily in normal individuals (e.g., during exercise) up to 170 L/min. This is maximal voluntary ventilation, previously called maximum breathing capacity.

Lung volumes are often measured to assess the integrity of pulmonary ventilation and also can give useful diagnostic information about the underlying disorder causing impaired pulmonary function. These measurements are made by having the subject breath into a spirometer. The forced vital capacity (FVC), the amount of air which can be expired after a maximal inspiratory effort, is frequently measured clinically as an index of pulmonary function. Weakness in the respiratory muscles limits both the IRV and ERV giving rise to restrictive lung disease. Impaired expiratory muscle function increases RV and FRC and hence, TLC is often surprisingly normal despite severe weakness in respiratory muscles[68]. A reduction

in the forced expiratory ratio (FEV_1/VC) is theoretically possible with severe expiratory muscle weakness but not observed clinically, implying normal airway conductance. However, peak expiratory flow is impaired[78]. A major clinical effect of expiratory muscle weakness is reduced efficacy of cough.

The strength of the respiratory muscles can be measured indirectly by measuring the pressure generated during maximal voluntary inspiratory and expiratory manoeuvres. The value of these tests is compromised by being effort dependent and in some individuals where weakness of bulbar muscles or corticospinal tract dysfunction, impairs the ability to generate a maximum voluntary effort. In such situations, non-volitional tests by electrical or magnetic stimulation are preferable. However, such tests are currently of research interest only and are not routinely used in clinical practice[78].

The typical breathing pattern in a patient with respiratory muscle weakness shows a small tidal volume and rapid frequency, which implies that a large proportion of the total ventilation is wasted in the anatomical dead space. The PO_2 is normal or only slightly reduced and the PCO_2 is often slightly reduced in the presence of mild weakness[79]. The presence of daytime hypercapnia usually implies severe weakness and poor prognosis.

1.13.3) Mechanics of cough

Cough is generated through the breathing muscles and is essentially a modified breathing pattern. It can be initiated either voluntarily or by the mechanical irritation of cough receptors. Cough receptors are located primarily in the central airways (larynx, trachea and carina) and gradually decrease in density towards more distal airways. The predominant cough receptors in distal airways are chemical receptors (sensitive to noxious gases and fumes). In response to airway irritation (chemical or mechanical), afferent nerves activate the brain stem respiratory centre to generate the cough breathing pattern. The vagus nerve is the primary afferent pathway to the cough centre while the phrenic nerve and other thoracic motor nerves make the efferent limb of the cough reflex[80].

Cough begins with a deep inspiration (inflating lungs to 85-90% of total lung capacity) and closure of glottis, which then suddenly opens having gained pressure from contraction of respiratory and abdominal muscles, and the cough is released in the form of a forceful

expiration (Figure 4). The expiratory airflow produces a shearing effect on the mucus lining the airways. Hence, inspiratory, expiratory and glottic muscle function is required for an effective cough and weakness in any of these muscles can affect peak cough flow (PCF). The normal cough volume is 2.30±0.5 L. An effective cough can generate a PCF of up to 720 L/min. Cough effectiveness is sub-optimal when PCF is less than 270 L/min.

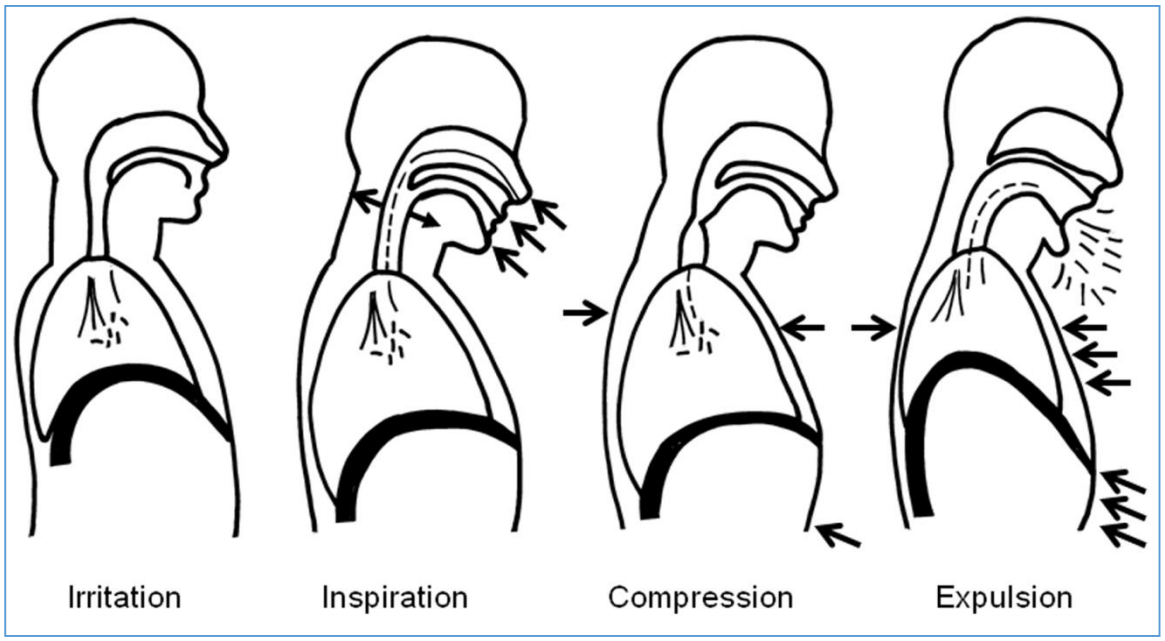


Figure 4: Four phases of a normal cough

1.14) Respiratory complications in Motor Neurone Disease

As with most other skeletal muscles of the body, the respiratory muscles are also affected in MND. Due to neuronal degeneration, there is a reduced number of motor units within the respiratory muscles and hence reduced force of contraction. Also, interruption of the descending upper motor neurone input from the cerebral cortex impairs voluntary control of breathing. Patients develop restrictive lung disease and hypoventilatory respiratory failure.

As the disease progresses there is progressive reduction in exercise tolerance and dyspnoea occurs with minor physical activity, eventually leaving the patient short of breath at rest. Respiratory function is an important independent predictor of both quality of life[81] and survival[82]. Respiratory complications are the leading cause of mortality and morbidity in MND[83]. The following mechanisms contribute to the pathophysiology of respiratory morbidity in MND.

1.14.1) Nocturnal respiratory insufficiency: Respiratory muscle weakness is often unmasked during sleep, especially during the rapid eye movement (REM) phase. During REM sleep there is tonic and phasic inhibition of postural muscles, so that all muscles of ventilation are inactive except the diaphragm (a normal physiological phenomenon). Hence, if the diaphragm is weak due to neuromuscular disease, hypoventilation develops in REM sleep, despite continuing normal ventilation in NREM sleep and while awake. The consequences of hypoventilation are oxygen desaturations and hypercapnia. Also, the supine position is mechanically disadvantageous for the diaphragm. In the supine position abdominal viscera push a weak diaphragm upward, leading to reduced lung expansion. This is not the case while standing when the diaphragm is helped by gravitational descent of the abdominal viscera. As the disease progress, hypoventilation extends into NREM sleep. There can be a great variation in the duration of this transition from REM related hypoventilation to hypoventilation in both REM and NREM. The development of hypoventilation in NREM usually indicates that the progression to daytime-awake state hypoventilation is likely to occur soon. The presence of an intercurrent event like a lower respiratory tract infection or a pulmonary embolism may accelerate this transition. In established respiratory failure the derangement in blood gases is characteristically worst during sleep. The quality of sleep is poor with only short fragments of REM and NREM sleep scattered between multiple arousals.

1.14.2) Abnormalities in central respiratory control: Abnormalities in central respiratory drive may play a role in the pathophysiology of respiratory dysfunction in MND. Nocturnal hypercapnia reduces the pH of the CSF because of accumulation of CO_2 in the CSF, which may in turn reduce the central respiratory drive[84]. Patients with evidence of bulbar involvement are more likely to have periods of central apnoea, which occur particularly during non-REM sleep.

1.14.3) Bulbar weakness: Cranial nerves IX, X and XII innervate the bulbar muscles which control speech, swallowing and maintain a patent airway during breathing. During inspiration, if upper airway muscles contract less than the thoracic muscles, the upper airway will narrow or collapse. This is because the sub atmospheric pharyngeal pressure generated by inspiratory muscles is not counterbalanced by adequate dilatory activity of upper airway muscles[85]. Poor bulbar function causes sleep disruption, independent of respiratory muscle weakness, from an inability to maintain a patent upper airway, especially during REM sleep. Obstructive sleep apnoea has been reported in 17-76% of patients with MND[86]. Bulbar weakness also impairs the ability to generate an effective cough by preventing effective closure of the glottis to generate sufficient intra-thoracic pressure.

1.14.4) Inability to cough effectively: Respiratory muscle weakness not only impairs ventilation but also impairs the ability to generate an effective cough. Cough is an important defence mechanism, clearing the airways of excessive secretions, airborne particles and creating a reflex mechanism preventing aspiration of pharyngeal contents. Inability to expectorate predisposes to recurrent chest infection. Damage to the lung parenchyma and bronchial tree reduce airway velocity during expectoration which in turn further compromises the effectiveness of cough. A weak cough is also associated with poor outcome in MND patients[87].

1.14.5) Recurrent chest infections: Weak breathing effort prevents aeration of the distal airways, leading to basal atelectasis which predisposes to pneumonia. Aspiration and then inability to clear airways due to a weak cough further contribute to the tendency to chest infections which are the commonest cause of hospital admissions in patients with respiratory muscle weakness. Recurrent chest infections also contribute to loss of pulmonary compliance.

1.14.6) Loss of pulmonary compliance: Periodic hyperinflation of the lungs is required to prevent peripheral atelectasis. Inability to take deep breaths due to the weakness in the respiratory muscles results in chronic microatelectasis and loss of lung elasticity, thus causing loss of pulmonary compliance[88]. Sleep may contribute to atelectasis and loss of lung volume due to reduction in tidal volume during sleep. Loss of movement also causes ankylosis in the rib cage joints causing an abnormally stiff rib cage and hence reduced compliance of the chest wall[89]. The reduction in lung compliance is reflected in the reduction in FVC and lung volumes.

1.14.7) Acute and chronic respiratory failure: Although chronic respiratory failure develops insidiously over time, acute respiratory failure is generally precipitated by intercurrent chest infections and blocking of the airways by mucus plugs. During chest infections, already impaired pulmonary function is further compromised by airway mucus plugging which may result in partial or complete collapse of the lung[90]. Worsening respiratory failure may require admission to the intensive care unit and intubation or tracheostomy[91]. Respiratory failure with or without bronchopneumonia is the usual cause of death in patients with MND.

1.15) Respiratory assessment in Motor Neurone Disease

Periodic assessment of respiratory function is important in motor neurone disease, to inform prognosis and plan timely intervention with respiratory support measures. The UK National Institute for Health and Clinical Excellence and American Academy of Neurology recommend regular screening for respiratory failure, following a diagnosis of ALS. The following clinical and laboratory measures may be used.

1.15.1) History: Disturbed sleep, due to episodes of hypoventilation, is one of the earliest symptoms of respiratory insufficiency. The symptoms of "sleep fragmentation" include nocturia, nightmares, unrefreshing sleep and daytime somnolence. Symptoms of CO_2 retention include morning headaches, poor appetite, fatigue, cognitive dysfunction and, as a result, poor quality of life. Taking a history from a partner or carer can be informative as they may be more aware than the patient of frequent arousals during sleep. With disease progression, patients may develop exertional dyspnoea, orthopnoea, dyspnoea at rest and anxiety associated with the feeling of breathlessness. Many MND patients prefer to sleep upright to counter orthopnoea. Patients with MND may have limited mobility due to muscular weakness and hence quantifying exertional dyspnoea may not be possible.

In a study performed by Just *et al.* the supine Borg dyspnoea score was used to predict respiratory muscle weakness in MND patients[92]. It can be used where tests of respiratory function cannot be performed due to lack of equipment or poor patient co-operation. Also, it can be equally useful in bulbar and limb subgroups of MND. A supine Borg score of ≥ 3 has a sensitivity of 80% and specificity of 78% to predict severe inspiratory muscle weakness (defined as SNIP ≤ 40 cmH_2O). The change over time of the Borg score reflected that of SNIP, however no linear correlation was found between mean nocturnal SpO_2 and the Borg score.

1.15.2) Examination: Clinical signs of respiratory insufficiency include tachypnoea and use of accessory muscles of breathing at rest, weak cough and sniff, reduced chest expansion and abdominal paradoxical movements (inward movement of abdomen on inspiration, which indicates marked weakness of the diaphragm). These clinical signs may not be present until respiratory muscle strength is reduced by 75%[93]. Signs of hypercapnia include flushed skin, warm peripheries, bounding pulse, asterixis, high blood pressure and bradycardia and

drowsiness with optic disc swelling in extreme cases. However, respiratory failure, may be present without any clinical marker of respiratory insufficiency[94].

1.15.3) Chest X-ray: A chest X-ray has limited role in the assessment of the respiratory system in the patients with MND. It may be helpful to exclude acute lung pathology in a patient presenting with acute respiratory impairment**.** Also, an elevated diaphragm on a chest x-ray may imply diaphragmatic weakness. Diaphragm movement may be assessed using fluoroscopy during inspiratory manoeuvres such as a short sharp sniff. Similarly, reduced diaphragmatic movement may be detected on ultrasonography.

1.15.4) Blood gases: Impaired ventilation is reflected in rising carbon dioxide and worsening acidosis in the blood and hence arterial blood gas analysis is required to confirm or exclude respiratory failure in suspected patients. Partial pressure of carbon dioxide (PCO_2) can be detected transcutaneously, along with oxygen saturation, with a probe attached to the ear lobe (TOSCA monitor). Normal day time PCO_2 reflects sufficient ventilation, however nocturnal hypoventilation cannot be excluded rather nocturnal blood gases should be considered worse than the day time readings. In order to measure what is happening to breathing during sleep, nocturnal studies are required. Overnight pulse oximetry can reveal nocturnal hypoventilation as indicated by episodes of desaturation. It has a particular advantage of being able to be done at the patient's home, however it cannot substitute for a more detailed evaluation by polysomnography[95]. Venous bicarbonate and chloride may be used as a compromise where obtaining an arterial sample is difficult. Venous bicarbonate is raised as a compensatory measure to combat respiratory acidosis and venous chloride is reduced to maintain the anion gap. Patients with a normal day time PCO_2 but raised bicarbonate invariably have nocturnal hypercapnia[96].

1.15.5) Polysomnography: Sleep studies or polysomnography are very useful and allows one to compare different phases of sleep with respiratory muscle function, pulse rate and oxygen saturation. It also helps to differentiate the cause of desaturation which might be obstructive (in patients with bulbar weakness) or hypoventilatory. It is important to delineate the exact cause of sleep disordered breathing, as one pattern of respiratory failure may respond to CPAP and the other with BiPAP. Full polysomnography however, requires a hospital admission

and skilled analysis. Polysomnographic indices (apneas and hypopneas) have shown weak correlation with quality of life[81]. However, nocturnal desaturations have prognostic value (mean SpO_2 < 93% associated with mean survival of 7 months vs. 18 months when mean SpO_2 > 93%)[97]. Polysomnography may allow early introduction of ventilator support when forced vital capacity may be preserved[98]. Whether sleep studies should be part of routine monitoring of patients with respiratory muscle weakness is controversial, as the value of early detection of nocturnal breathing abnormalities has not been established.

Non-Invasive-volitional tests of respiratory muscle function:

1.15.6) Vital capacity (VC) both sitting and supine: Vital capacity is measured using a spirometer (Vitalograph®) with the patient blowing into a face mask or a mouth piece after a deep inspiration. It is dependent on the strength of both inspiratory and expiratory muscles. Though very easy to perform in the clinic setting and at home (and hence its widespread use), it is rather non-specific and insensitive measure of respiratory muscle weakness and is affected by many systemic, pulmonary and cardiovascular diseases[99]. It is dependent on the patient's voluntary effort and has strong limitations when used in patients with bulbar and pseudobulbar palsy, who cannot blow effectively. Furthermore, it does not correlate with PCO_2 well, a VC of as high as 78% may be associated with hypercapnia[100]. A low VC can be used as a screening method to prompt further investigations. The rate of decline of VC is a prognostic factor in MND[101]. A drop in VC by ≥ 25% in the supine position indicates significant diaphragmatic weakness[102].

1.15.7) Maximum insufflation capacity (MIC): Maximum insufflation capacity is the volume of air that can be retained in the lungs with a closed glottis. It reflects the strength of oropharyneal and laryngeal muscles and hence can be used as a marker of the integrity of bulbar musculature[88].

1.15.8) Maximal inspiratory pressure (P_IMax): P_{Imax} is a test of inspiratory muscle strength. It is recorded from functional residual volume (FRC), using a pressure transducer, a mouth piece and a nose clip applied, as the highest inspiratory pressure maintained for one second. The test has advantages in that it is non-invasive and can be readily measured in the clinic with a

portable device, but its usefulness is limited because it is hugely dependent on the patient's effort and co-operation. The normal value is >80 cmH_2o, however there is a wide inter-subject variability[103]. Consensus guidelines suggest that a PImax of < 60 cmH_2O indicates the need for NIV in progressive neuromuscular disorders[104].

1.15.9) Maximal expiratory pressure (P_EMax): P_EMax is a test of expiratory muscle strength. It is recorded using the same equipment as P_iMax and has similar limitations. The normal value is >100 cmH_2O. It has the advantage of specifically assessing expiratory muscle power, although elastic recoil of the lungs and chest wall contributes to the reading obtained.

1.15.10) Peak cough flow (PCF): PCF is easily recordable with the patient coughing into a face mask attached to a peak flow meter. Expiratory muscle weakness is largely responsible for a reduction in PCF. PCF of at least ≥ 160 L/min is required to clear airway secretions. PCF is a useful measure to identify patients at high risk of developing acute respiratory failure as patients with PCFs < 160 L/min are more prone to develop chest infections[83]. In several studies cough performance has been assessed by PCF measurement[105]. PCF has also been suggested as a predictor of survival, patients with a mean PCF above 337 L/min had a significantly greater chance of being alive at 18 months[106]. Peak cough flow has value in predicting successful extubation in patients with neuromuscular disorders who required invasive respiratory support.

Invasive volitional tests of respiratory muscle function:

1.15.11) Sniff nasal inspiratory pressure (SNIP): SNIP estimates diaphragmatic strength. It correlates with the transdiaphragmatic pressure ($r=0.9$, $p < 0.01$)[107]. Sniff is a natural manoeuvre and hence is easy to perform, using a probe in the patient's nostril while s/he takes a sharp sniff[108,109]. The manoeuvre starts from the end expiratory volume after a quiet breath. It may be superior to VC in assessing respiratory muscle strength in MND patients[100]. A pressure of 25 cmH_2O (32%) or less is highly predictive of respiratory failure and median survival of 3 months[58]. However, values are affected by anatomical abnormalities like nasal polyps and septal defects and the patients' voluntary effort. Even in healthy subjects, total nasal resistance usually is low in one naris and high in the other[67].

1.15.12) Transdiaphragmatic pressure (Pdi): Pdi can be calculated using pressure probes in the oesophagus and stomach as oesophageal (Poes) and gastric (Pga) pressures reflect pleural and abdominal pressures respectively. The strength of diaphragm contraction is reflected as a fall in Poes and a rise in Pga. Being an invasive test, it may not be well tolerated by some patients.

1.15.13) Sniff Poes and Sniff Pdi: Oesophageal pressure during a maximal sniff is often regarded as the best measure of inspiratory muscle strength[110]. The normal range is 74-135 cmH_2O. As with SINP, sniff Poes is affected by nasal abnormalities. One study proved Sniff Pdi of 30 cmH_2O as a highly discriminatory test to detect hypercapnia with a sensitivity and specificity of 90 and 87% respectively.

Invasive non-volitional tests of respiratory muscle function:

The tests of respiratory muscle function described above are dependent on the patients' effort. There are a few validated non-volitional tests, but they are invasive and currently limited to research and are not routinely used in clinical practice.

The strength of a muscle can be assessed non-volitionally by stimulating the nerve supplying it, by electric current or magnetic field. Magnetic stimulation is less painful than electric stimulation and tends to give more reproducible results given the wide range of stimulation parameters available[111].

1.15.14) Unilateral magnetic stimulation of the phrenic nerve (UMS): The phrenic nerve innervates the diaphragm and hence magnetic stimulation of the phrenic nerve can be used to assess diaphragmatic strength. With oesophageal and gastric balloon catheters in situ, the technique stimulates the phrenic nerve with a magnetic coil placed over the cervical roots of the phrenic nerve at the spinous processes of the 5^{th}-7^{th} cervical vertebra. Care is required to obtain maximum contact, which may be difficult in obese subjects and those with skeletal abnormalities like ankylosing spondylitis.

1.15.15) Twitch transdiaphragmatic Pressure *(T_wPdi):* T_wPdi is invoked by phrenic nerve stimulation. Since this technique is independent of the patient's efforts, it is particularly useful

in patients with bulbar weakness. However patients may find the placement of oesophageal and gastric balloons unpleasant. The normal value is 31 cmH_2O[112]. Since accessory muscles of breathing are activated by simultaneous stimulation of neighbouring cervical nerve roots, T_wPdi may reflect a contribution from extra-diaphragmatic muscles.

Non-invasive non-volitional tests of respiratory muscle function:

1.15.16) Twitch mouth pressure *(T_wPmo):* Experiments have been done by Mustafa *et al.* to develop a non-invasive non-volitional test for respiratory muscle function[113]. They demonstrated that in healthy subjects with the application of continuous positive airways pressure, mouth pressure reflects oesophageal pressure following UMS, thus avoiding the need for oesophageal and gastric balloons. However, they recommended that the technique needs refining for MND patients.

Neurophysiological techniques for respiratory assessment

1.15.17) Phonomyography: Vibrations and low frequency sounds produced during the contraction of skeletal muscles can be recorded with a microphone attached to the skin. The signal thus recorded is called a phonomyogram. This sound signal is directly proportional to the tension developed within the test muscle. Diaphragmatic function can be assessed by recording the phonomyogram during unilateral magnetic stimulation. Although this technique is still under study, it appears attractive because it is non-invasive[114].

1.15.18) Electrophysiological techniques: The electrophysiological measures of respiratory muscle function are spontaneous EMG and the compound motor action potential of the diaphragm (CMAPdi) following supramaximal stimulation of the phrenic nerve. A reduced CMAPdi reflects reduced diaphragmatic force of contraction. CMAPdi may be recorded through needle electrodes, oesophageal electrodes and surface electrodes. Needle electrodes and oesophageal electrodes have the benefit of directly accessing the diaphragm but are unpleasant techniques from the patients' point of view, limiting their clinical use[115].

1.16) Prevention and management of respiratory morbidity

Without active management of respiratory symptoms, the majority of patients with MND die within 3-6 months from the onset of neuromuscular respiratory failure. Provision of non-invasive ventilation has been established as a supportive measure for domiciliary treatment of respiratory failure. Pulmonary morbidity and mortality can be further prevented by identifying patients with poor peak cough flows and teaching them cough augmentation techniques and providing prompt treatment of chest infections[116]. Influenza and pneumococcal vaccination and avoiding contact with people having upper respiratory tract symptoms may help to prevent chest infections. Control of excessive saliva and thick mucus with medicines like hyoscine butyl bromide and carbocisteine (mucolytic) may also help symptomatically and in the prevention of chest infections. Oxygen supplementation is not recommended for MND patients as it can abolish the hypoxic drive of respiration and make hypercapnia worse and hence its role is limited to patients having ventilatory support in the hospital setting. A higher rate of pneumonia and hospitalization was found in a study of neuromuscular patients receiving oxygen therapy[117].

1.16.1) History of mechanical ventilation

Galen (129-200 AD), a roman physician was the first to describe mechanical ventilation: “If you take a dead animal and blow air into its larynx (through a reed or cane), you will fill its bronchi and watch its lungs attain the greatest distension”[118].

In 1664, Hooke demonstrated dissection on an anaesthetised dog while still keeping him alive by placing a pipe in his trachea and ventilating the dog with a pair of bellows, powered manually. In 1669 Lower performed an experiment by placing a cork in an animal’s trachea and found that arterial blood appeared like venous. Arterial blood became bright red again by removing the cork and ventilating the lungs with a bellows. In 1744, Tossach successfully saved a life of a drowning victim with the technique of mouth-to-mouth ventilation. In 1760, Buchan suggested “an opening in the wind pipe” when air cannot be inhaled through month or nose. Its life saving value was further demonstrated by Trousseau in 1833 on patients with diphtheria. In 1776, Hunter advocated the use of double bellows for artificial ventilation. The first to blow fresh air into the lungs and the second to suck out stale air. In the same year

Cullen suggested using tracheal intubation and bellows ventilation for resuscitation. In 1780, Chaussier developed a simple bag and face mask for artificial ventilation[119].

However, positive pressure ventilation was abandoned due to the risk of pneumothorax and techniques were developed for negative pressure ventilation. First tank respirator was developed in 1832 by Dalziel of Scotland. Over the next fifty years many other devices (rocking bed, poncho-wrap, tortoise shell ventilator) were invented for negative pressure ventilation. These devices employed negative pressure generated through a mechanically produced vacuum to facilitate inhalation and positive pressure compression to the chest to allow exhalation.

However, it was not till 1928 when the first clinically useful negative pressure ventilator "Iron lung" was developed by Drinker-Shaw. It saved several lives during polio epidemics. The availability of electricity allowed the development of electric motors to power ventilators which helped to treat chronic respiratory insufficiency in the polio survivors.

Positive pressure ventilation was re-introduced in 1950 when its use was established in thoracic surgeries which involved opening the chest and hence inducing pneumothorax. During the 1952 polio epidemic in Copenhagen, Ibsen suggested that hypoventilation, hypercapnia and respiratory acidosis were the cause of high mortality in polio patients with respiratory paralysis. Medical students were employed to manually ventilate the polio patients with respiratory paralysis[120]. These patients had better outcome then patients ventilated with iron lung. Since then several practical ventilators have been developed that reliably deliver pre-set volumes and pressures. Intensive care units have been established to treat acute respiratory failure. Negative pressure ventilation was progressively abandoned.

Non-invasive negative pressure ventilators were once again used in early 1980s when their intermittent (nocturnal) use was found to be beneficial in patients with neuromuscular disease with symptoms of chronic hypoventilation. Efforts were made to develop portable and user friendly machines[121].

During 1970s switching from non-invasive negative pressure ventilation to non-invasive positive pressure ventilation was attempted with variable success. The technique required

the use of uncomfortable face masks and hence required considerable co-operation from the patients and nursing staff. Over the years comfortable face masks became available.

In 1981, Sullivan and colleagues used nasal continuous positive airway pressure in patients with obstructive sleep apnoea. Later on intermittent positive pressure ventilation was also applied using comfortable nasal interfaces. In the past two decades portable and inexpensive non-invasive positive pressure ventilators have been developed for domiciliary use in patients with chronic respiratory insufficiency due to neuromuscular weakness or pulmonary disease[122].

1.16.2) Non-invasive ventilation in Motor Neurone Disease

The introduction of Non-Invasive Positive Pressure Ventilation (NIPPV) via mouthpiece or by nasal or oronasal interfaces, transformed the care of respiratory failure in neuromuscular disorders[123]. Respiratory function is strongly and independently related to the quality of life (QoL) in MND[81], hence it was felt that supporting respiratory function with NIV may palliate symptoms of chronic hypoventilation, improve QoL and prolong survival. NIV was pioneered by Rideau *et al.* in France and by Bach *et al.* in the United States in 1980s[121,124]. Since then, a number of prospective studies and randomized clinical trials have now demonstrated the role of NIV in symptom relief, enhancing QoL and survival in patients with MND[125-129]. Oppenheimer *et al.* performed a prospective study involving 75 MND patients on home ventilation, twenty five being on non-invasive ventilation. They reported that NIV was well tolerated in patients with predominantly limb weakness, providing good relief of respiratory symptoms and such patients were happier than patients using tracheostomy ventilation. Five patients had significant bulbar dysfunction and were intolerant of NIV and found the treatment ineffective[130]. Similarly Aboussouan *et al,* in an observational cohort study found that survival was better in MND patients who were compliant with NIV. Severe bulbar dysfunction was associated with intolerance of NIV. Kleopa *et al.* conducted a retrospective review of 122 MND patients who were offered NIV. The patients who refused NIV and who were intolerant of NIV acted as a control group. The two groups were comparable in baseline variables. They reported that survival was significantly associated with the duration of NIV use and FVC declined more slowly in patients using NIV. The issue of impact of NIV on quality

of life of MND patients was addressed by Lyall *et al.* who in a prospective study, using Short form 36 (SF-36, a generic QoL assessment tool) showed that there was improvement in the "vitality domain" of patients treated with NIV, compared to matched non-ventilated controls[128]. None of these studies have reported any negative effect of NIV on pulmonary function.

The first prospective controlled trial of the effect of NIV on QoL and survival in MND was conducted by Pinto *et al.* in 1995[126]. An obvious limitation of this trial was the very small number of patients (10 in each arm). However, they demonstrated a significant improvement in total survival time ($p < 0.004$) and in the survival from the onset of diurnal gas exchange disorder ($p < 0.006$). Bourke *et al.* in 2006 demonstrated through a randomised controlled trial involving 41 MND patients, a median survival benefit of 205 days and improved quality of life in patients with good bulbar function. QoL was assessed with both generic (Short form 36) and respiratory disease specific (Sleep apnoea quality of life index and chronic respiratory disease) questionnaires. Patients with severe bulbar dysfunction found it difficult to tolerate NIV and had no survival benefit. The length of survival and QoL was strongly related to NIV compliance. Although moderate to severe bulbar involvement was associated with poor compliance and hence less improvement in QoL, improvement in sleep related symptoms was observed in such patients. Hence, NIV is still offered to patients with severe bulbar dysfunction, modified with a suitable interface and optimal ventilator settings to prevent air leaks. However, less than 30% of patients with significant bulbar weakness tolerate NIV. Another study showed no significant difference in survival in patients with severe bulbar disease following treatment with NIV, compared to those who were intolerant of NIV[131].

Recent studies are encouraging relatively early use of NIV, to achieve the maximum benefit[132, 133]. In this regard, sleep disordered breathing is the most useful criterion even in the absence of day time hypercapnia[86]. Carratu et al. recommended that MND patients with FVC < 75% of predicted should be admitted for polysomnography and NIV should be prescribed to those proven to have nocturnal hypoventilation. They found evidence of sleep disordered breathing in all patients with FVC < 75% of predicted[134]. All such patients were offered NIV and one year survival rates were significantly higher in well compliant patients than those with similar FVC who refused or were intolerant of NIV. Also, the median rate of FVC decline was slower in patients who tolerated NIV compared to those who were intolerant of NIV. Similarly, Lechtzin

et al. initiated NIV in MND patients with FVC < 65% and reported a significant improvement in survival[133]. However, offering NIV at a very early stage for mild impairment of respiratory function is associated with a higher failure rate due to poor patient compliance[134]. In the UK recently published NICE guidelines have served the need to standardize the provision of NIV to patients with MND in the UK. According to these guidelines any patient with a FVC of less than 50% of predicted alone or less than 80% of predicted with symptoms or signs of respiratory impairment should be evaluated further and considered for NIV. Also any patient with oxygen saturation of less than 94% should be evaluated further with an arterial blood gas analysis and NIV considered if the PCO_2 is greater than 6 kPa or if the symptoms of respiratory insufficiency are present (http://guidance.nice.org.uk/CG105/Guidance).

There are several unanswered questions relating to the long term use of NIV:

- **When to stop NIV therapy:** Once patients with MND enter the terminal phase of their illness, the role of NIV in the palliative care of these individuals is uncertain and may potentially be detrimental to quality of life, creating an obstacle to feeding and communication. Attention to symptomatic treatment needs may be more important in this phase of the illness. However, there are no studies on the effect of NIV at the end of life and the burden of this intervention perceived by the patients and carers during the terminal phase of the disease and hence there are no evidence based guidelines about when and how to stop NIV. Indications to stop NIV may include unacceptable quality of life and patient's wishes.
- Burden for the caregiver: Studies on the carers of patients using NIV suggest that they may have an increased incidence of stress and depression[129].
- Factors influencing the effects of NIV: Little is known about the factors that influence the effect of NIV on QoL and subsequent survival.
- Long term physiological effects: There are insufficient data on the long term physiological effects of NIV.

Some patients use NIV for 16 to 24 hours/day. This requires special attention to assisted coughing and secretion removal to avoid recurrent chest infections as a result of inability to cough effectively. Proper management of secretions has a pivotal role in the success of NIV. It is therefore important to combine NIV with cough augmentation techniques.

1.16.3) Invasive ventilation in Motor Neurone Disease

Invasive ventilation involves placement of a tracheostomy tube which can be used to deliver air into the lungs and clear secretions from the upper airways. Tracheostomy ventilation (TV) may be considered as an option for ventilation in patients with severe bulbar dysfunction who are unable to tolerate NIV. TV may also be considered even in successful users of NIV when, with the continued progression of respiratory and bulbar muscle weakness, effective ventilation cannot be provided with non-invasive means. Apart from being an option for ventilation, tracheostomy may also be required in patients with severe bulbar dysfunction to protect the airway from recurrent aspiration of saliva[135]. A recently published study involving 38 patients of ALS who had tracheostomy, reported one year survival rate of 78.9%, with a mean survival of 10.39 months[136]. Studies on quality of life after tracheostomy have reported positive views of patients about tracheostomy and acceptable quality of life[137,138].

TV is usually provided with a volume cycled ventilator through an uncuffed tube. TV does not involve a face mask (hence there is no risk of claustrophobia or facial discomfort) and allows direct suctioning of secretions. However it is associated with several problems like bleeding and infection at the tracheostomy site (tracheitis), recurrent pneumonia, tracheoesophgeal fistula and risks the patient being trapped in a paralysed body - "locked-in state" or "ventilator entrapment"[139,140]. With an uncuffed tube, patients may continue to talk and eat, but they run the risk of aspiration. Also, air leaks may cause discomfort or compromise the effectiveness of mechanical ventilation. Uncuffed tubes may have to be replaced by cuffed tubes when effective ventilation may not be achieved despite increasing the ventilator volumes[141]. With a cuffed tube the patients will lose the ability to vocalise, a clinical situation that may get worse when eye movements are also lost. In addition, a cuffed tracheostomy tube risks tracheal necrosis secondary to cuff overinflation. TV also requires extensive resources (24 hour nursing care and frequent hospitalizations) and can reduce the quality of life of the carer[130]. It may prolong life in the face of increasing disability and dependency and hence quality of life may not be sustained in the advanced stages of the disease. In the US few patients with MND take this option due to the generally negative attitude of the physicians and lack of coverage for invasive ventilation by most health insurance policies. Similarly, TV in MND is not encouraged in Europe considering the progressive and incurable nature of MND and the high cost involved in caring for a patient with tracheostomy[142]. In

Japan, however, the predominant form of ventilation offered to the patients with MND is TV and the cost is fully covered by the government and medical insurance[143]. According to one Japanese survey 30% of patients in Japan took this option[144].

Published literature shows that when informed in advance about the option of TV to prolong life; most patients with MND refuse tracheostomy. In the UK, in most instances, tracheostomy is performed in an emergency following an endotracheal intubation, carried out during a life threatening acute respiratory tract infection. Rarely, the diagnosis of MND may have not been made and patients may present to the emergency department with respiratory failure of unknown cause and undergo tracheostomy[41].

1.16.4) Diaphragm Pacing in Motor Neurone Disease

Diaphragm Pacing (DP) is a technique of assisted ventilation using intramuscular electrical stimulation of the diaphragm to produce contractions. It was initially developed as a mean of providing ventilator support to patients with high spinal cord injury[145]. In such patients it has allowed a reduction in their time on mechanical ventilation or removed its need. The use of diaphragm pacing has been explored in the patients with MND with respiratory failure. However, there are limited data about its efficacy in these patients and this technique is still in an experimental phase.

The modern NeuRX RA/4 DP system consists of four electrodes which are implanted laparoscopically on to the abdominal surface of the diaphragm (two in each hemi-diaphragm). The best site for electrode placement is established at surgery by mapping the diaphragm to locate the phrenic motor points[146]. The system only works if the diaphragm muscle retains some degree of innervation. The leads are tunnelled subcutaneously to a suitable exit site, usually in the upper abdomen. A pocket size battery operated external stimulator delivers the stimulus pulses and provides respiratory movements (Figure 5). The current cost of the equipment and surgery is around £16,000. Onders *et al.* have reported that general anaesthesia can be safely performed in patients with MND having laparoscopic surgery for diaphragm pacing[147]. They reported experience of diaphragm pacing in a series of 51 patients with FVC readings ranging from 20% to 87% predicted with no failure to extubate or 30 day mortality. Diaphragm pacing has several potential advantages over mechanical ventilation.

Most patients are able to eat, talk and mobilise freely while being paced, however careful post implantation follow up is required.

A US Food and Drug Administration approved clinical trial of diaphragm pacing in MND is under way which will provide information about the safety, tolerability and efficacy of diaphragm pacing in patients with MND. A randomised controlled clinical trial (DiPALS) is underway in the UK, to fully evaluate the place of diaphragm pacing in patients with MND. Clinical recommendations about the efficacy of diaphragm pacing in MND await the conclusion of these trials.

1.16.5) Assisted cough in Motor Neurone Disease

Assisted cough techniques have been developed to help patients with respiratory insufficiency caused by neuromuscular disease. These techniques may include the combined inspiratory and expiratory muscle aids or either inspiratory or expiratory muscle aids alone. However, in most patients with MND both inspiratory and expiratory muscles are weakened [148], and hence theoretically it is best to employ both inspiratory and expiratory muscle aids for effective cough augmentation. Tzeng and Bach developed a home protocol combining NIV with cough assist techniques and followed up the patients. They concluded that patients using the protocol had significantly fewer hospitalizations per year and days hospitalized per year[83]. These authors suggested that tracheostomy is required to extend survival in patients unable to achieve an assisted PCF > 160L/min[149]. In the great majority of patients assisted PCF of > 160 L/min can be attained except in patients with severe bulbar disease[150].

1. ***Manual chest physiotherapy (CPT)*** is traditionally used during chest infections to hasten recovery. The aim is to mobilise the secretions to help the patient cough them out. These techniques require considerable time (at least 30 minutes) and effort from the patient and can even cause episodes of desaturation[151]. Moreover an appropriately trained therapist is required. Physiotherapy can be combined with NIV to improve tolerance, however CPT on its own is unlikely to be sufficient to clear airway secretions in advanced neuromuscular respiratory failure in MND.

2. ***Forced expiratory technique (FET)*** has been used for decades to clear airway secretions[152,153]. It involves taking huffs (like a forced sigh) at low lung volumes to move secretions from the

peripheral airways and then a cough at full lung volume to clear the more proximal airways. Again, this technique has not been demonstrated to be sufficient on its own. It works on the principle that the airway walls collapse during expiration and helps to increase air flow velocity, thus providing the necessary shear velocity to bring sputum proximally. The benefits of this technique include that it does not require any equipment or assistance.

3. ***Manually assisted coughing (MAC)*** involves active expiration after a full inspiration while a physiotherapist assists coughing by applying pressure to the lower ribs and the abdomen (chest compression and abdominal thrust), thus increasing the expiratory driving pressure and compensating for expiratory muscle weakness. Sancho *et al.* reported that stable MND patients with PCF > 245 L/min were able to effectively clear secretions with MAC[154]. MAC may be less effective in obese patients, patients with severe scoliosis and patients with abdominal or thoracic conditions which may hinder proper hand placement. The technique should be used with caution in patients with stiff chest walls and osteoporotic ribs. Furthermore the frequent need of manually assisted coughing in patients with airway secretion accumulation may tire the patient and cause upper limb muscle strain in the carer. MAC may be detrimental in patients with sufficient unassisted PCF as it may interfere with spontaneous cough[155].

4. ***Breath-stacking technique*** uses an Ambu bag to deliver large breath volumes to the patient via a suitable interface. The lungs are inflated as fully as possible by stacking successive breaths i.e. holding them with a closed glottis. Once lungs are maximally inflated the patient quickly releases the compressed air volume under expiratory muscle force, thus generating a cough. To help patients, breath stacking can be combined with abdominal thrust or tussive squeeze applied by a carer or therapist. Assisted cough flow can be significantly improved by breath stacking. However, this is a difficult technique requiring reasonable respiratory muscle strength and co-ordination and may leave the patients exhausted. Furthermore, patients with bulbar muscle weakness may find it impossible to retain the volumes of air acquired by stacking, due to inability to close the glottis. However, in such patients one single deep breath with the Ambu bag may assist in coughing[156]. It has been demonstrated in several studies that adding MAC to breath stacking increases the benefit. However, if the VC is < 340ml, breath stacking and MAC may not be sufficient to produce a PCF of above 160 L/min and such patients may only benefit from an in-exsufflation device[157].

5. ***Mechanical Insufflator-Exsufflator (MI-E)*** or CoughAssist® (Philips Respironics, Murrysille, Pennsylvania) machine is a portable electronic machine which simulates cough by delivering alternative cycles of positive and negative pressure to the airways through a face mask. It can also be used with a mouth piece or tracheostomy. The positive pressure increases the inspiratory pressure, and the negative pressure increases the expiratory pressure. The PCF increase using a mechanical insufflation/exsufflation technique was more significant as compared to either MAC or breath stacking alone[158]. Furthermore, it was well tolerated by the patients. Bach suggested that applying an appropriately timed abdominal thrust during exsufflation enhances the effectiveness of MI-E[159]. The volume of air and PCF exsufflated using MI-E are comparable to those expulsed during normal adult coughing[159]. However the machine is expensive and evidence of its effectiveness is lacking from randomised controlled trials, which limits the widespread availability of this equipment for patients.

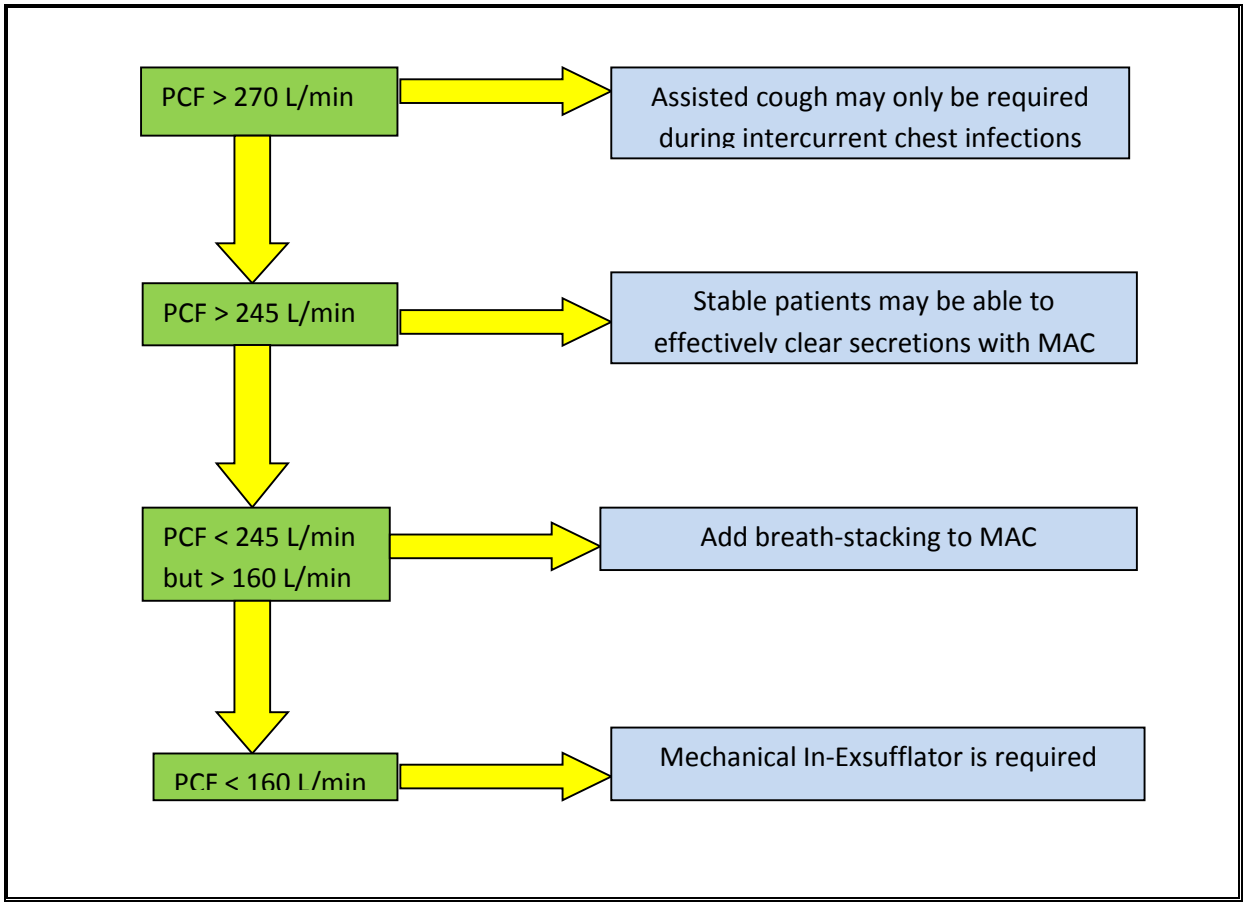
6. **Intrapulmonary percussive ventilator** has been used to remove secretions and relieve atelectasis in children and adults with neuromuscular disease[160]. The patient breaths through a mouth piece which delivers high flow pulsatile "bursts" (percussions). This causes internal vibrations within the lungs which promotes mobilization of secretions from the peripheral airways. However currently there are insufficient data to make a recommendation for clinical use[58].

7. **Modified active-cycle-of-breathing technique on NIV:** Volume ventilators can be used for breath stacking to increase inspiratory volume. However, no prospective or retrospective study has evaluated NIV as a lung volume recruiter in neuromuscular disease patients who use domiciliary NIV and require cough assistance. Fauroux et al investigated the effect of NIV as a cough augmentation technique in cystic fibrosis patients and reported far less fatigue when clearing secretions with the assistance of NIV[161]**.**

8. **High frequency chest wall oscillation (HFCWO):** High frequency chest wall oscillation with a chest-percussion vest has been successfully used in children with cystic fibrosis. However, studies involving patients with MND have shown mixed efficacy in altering pulmonary morbidity[160 162]. HFCWO was well tolerated, considered helpful by the majority of the patients and a trend towards slowing the decline of FVC was observed. However, the number of the

patients studied was too small to make any meaningful conclusions. The benefits of this technique include the fact that little effort is required by the subject and the fact that efficacy is technique-independent.

Toussaint *et al.,* worked on the measurable parameters of respiratory muscle strength which could help to predict which cough augmentation technique will benefit which patient[157]. It is helpful to know the limits of effectiveness, as under those limits a cough augmentation technique may not be effective. The results showed MAC to be beneficial for patients with a VC between 1030-1910 mL. Below these limits MAC may be ineffective. Breath stacking alone may benefit cough augmentation in patients with VC > 558mL and breath-stacking plus MAC helps to produce an effective PCF in patients with VC > 340mL. Patients with VC < 340 mL required a mechanical in-exsufflator for effective cough augmentation. The PCF did not increase any further with cough augmentation in subjects with mean expiratory pressure (MEP) > 50 cm H_2O. They concluded that patients with MEP > 34cm H_2O should cough better unassisted. The relationship between VC and the ability to benefit from a cough augmentation technique may reflect the degree of neuromuscular weakness which determines whether an individual patient is able to cope with the demands of a specific cough augmentation technique. Figure 5 provides an algorithm for the management of weak cough in MND based on the review of existing literature.[149,154,157,163]



PCF Peak Cough Flow
MAC Manually Assisted Cough

Figure 5: Suggested strategy for cough augmentation in MND

1.16.6) Literature review of the use of the breath-stacking technique and the MI-E

As this PhD work describes a randomised trial of the breath-stacking technique versus MI-E (chapter 3), the literature on these two cough augmentation techniques is discussed in more detail below.

1.16.6.1) Breath stacking technique (using the manual insufflator):

Breath-stacking is a technique to improve lung volume recruitment (LVR), hence it is also called lung volume recruiter or manual insufflator. The rationale behind its use is that the patients with weak inspiratory muscles cannot attain a sufficient inspiratory lung volume to generate a strong cough. The technique uses a self-inflating Ambu bag (Figure - 8) to aid inspiratory volume by "stacking" one breath on another, each held with a closed glottis without expiration, till maximum insufflation is achieved at which stage the patient coughs out forcefully. Breath stacking has been shown to improve inspiratory volume, correct basal atelectasis, enhance rib cage movement and improve voice volume[164]. The device has a one way valve, allowing air flow towards the patient to enhance inspiratory effort. The patient can be attached to the equipment with a mouth piece interface or a face mask interface. The mouth piece interface allows the patient to stop the treatment himself (by opening the mouth and dropping the mouth piece) and reduces the need of a carer to hold the face mask interface. The aim of breath stacking is to achieve Maximum Insufflation Capacity (MIC) and not to hyperinflate the lungs. It can be combined with a chest compression and/or abdominal thrust synchronised with the patient's coughing following maximal insufflation.

A review of the literature regarding the breath-stacking technique reveals very few studies whose design and methodology can be considered optimal. Anecdotal evidence from the ALS centres in Canada, where the technique is commonly used show that breath-stacking not only improves peak cough flow and airway mucus clearance, but also improves the patients' voice quality and the ability to protect their airway and hence reduces the risk of aspiration and choking during swallowing (http://www.irrd.ca/education). Maximum insufflation of the lungs also reduces microatelectasis and maintains mechanical compliance of the rib cage. Lechtzin et al. demonstrated in a prospective trial that supra-maximal lung inflation improves

lung compliance possibly by correcting peripheral atelectasis[89]. One study showed that PCF improved by 50 L/min after treatment with breath-stacking, and this improvement was sustained for about 30 minutes[165].

Cleary et al. studied the impact of breath stacking on the respiratory function and well-being of patients with MND, using a qualitative approach. 77.8% of the participants reported that breath-stacking helped them to clear their secretions and had a positive influence on their quality of life [166]. Bach *et al.* reported a case series of patients with Duchenne muscular dystrophy using glossopharyngeal breathing and breath-stacking to increase lung volumes. The patients with a maximum insufflation capacity (MIC) greater than vital capacity (VC) could effectively use breath stacking and achieve PCF of 289 +/- 90. Also, breath-stacking could delay and decrease daytime ventilator use in patients with Duchenne muscular dystrophy[167]. Brito *et al.* studied PCF in patients with Duchenne muscular dystrophy following chest compression, breath stacking and after breath-stacking and chest compression (combined technique). They reported no statistically significant difference in PCF achieved by chest compression and breath-stacking. However, with the combined technique, PCFs were significantly higher than those with either of the techniques used in isolation[163]. They recommended that breath stacking should be combined with chest compressions.

Breath-stacking equipment is easy to use, light weight and its low cost means that it could be made available to the patients early on in the disease. The drawbacks include the fact that some patients experience difficulty in using the technique, especially patients with poor bulbar function who cannot close their glottis and that it can be laborious and tiring for frail MND patients.

1.16.6.2) Mechanical In-Exsufflator (MI-E):

As described before the mechanical in-exsufflator (MI-E) is a portable electronic cough assist device currently marketed as CoughAssist® by Philips Respironics (Figure - 9). It simulates a normal cough by applying positive inspiratory pressure (insufflation) followed by a sudden shift to negative pressure (exsufflation) via an anaesthetic face mask. The rapid shift in pressure produces a high expiratory flow rate from the lungs and increases secretion clearance. The machine can generate a pressure of up to +60/-60 cmH_2O. As per the

manufacturer's guidelines a minimum pressure of +40/-40 cm H_2O is required to generate sufficient cough expiratory flows to allow clearance of respiratory secretions. However, initially the insufflation and exsufflation pressures are independently adjusted for the patient's comfort and then gradually increased.

MI-E is not new, it was reported in the early 1950s to have effectively removed radiopaque material and bronchoscpically inserted foreign bodies from the airways of anaesthetized dogs[168]. It was introduced in 1952 as a clinical device, Cof-Flator (OEM, Norwalk, Connecticut) during the poliomyelitis epidemic, to help patients supported by body ventilators. Barach and Beck studied the effects of MI-E in 103 acutely ill patients (72 with intrinsic lung disease and 27 with skeletal or neuromuscular diseases) and reported no adverse effects, despite the theoretical risk of rupture of an emphysematous bulla[169]. They reported a 55% increase in FVC following MI-E in patients with neuromuscular diseases in addition to clinical and radiographic improvement. However MI-E did not gain widespread popularity and fell into disuse with the popularity of invasive ventilation and suctioning via tracheostomy. It was not until 1990 when it was started to be used as an adjunct to non-invasive ventilation.

In 1993 the US Food and Drug Administration (FDA) approved MI-E for improving airway clearance. Several publications describing the physiological effects and clinical benefits of MI-E are authored by Professor Bach. These publications include a heterogeneous patient group including post-polio patients, children with muscular dystrophies, high spinal cord injury patients, patients with kyphoscoliosis and patients with ALS[116,170-172]. Bach has stressed that patients with neuromuscular respiratory failure, even with little or no FVC, can be successfully managed by non-invasive means, provided sufficient attention is given to assisted cough. He claimed that the ability to clear the airways of secretions is critical to obtain benefits from NIV[83] and tracheostomy may only be required when assisted PCEF of 160 L/min cannot be achieved[88]. He reported pulmonary complications and hospitalization rates in a retrospective study of 46 neuromuscular ventilator users[159]. There was a significant reduction in the episodes of pneumonia and days hospitalized following the use of non-invasive respiratory aids. PCEF was measured in a group of 21 patients, following an unassisted cough (1.81 ± 1.03 L/s), following a maximal insufflation using air stacking and glossopharyngeal breathing (4.27 ± 1.29 L/s) and with MI-E (7.47 ± 1.02 L/s). The PCEFs using MI-E significantly exceeded those produced by manually assisted coughing and none of the patients reported any complications

with the use of MI-E. The improvement in PCF is probably due to the recruitment of non-ventilated pulmonary zones and removing mucus debris. In another paper Bach et al. reported the use of manual insufflation and MI-E in post-poliomyelitis ventilator assisted individuals. They found that PCEF generated following maximum insufflation by air stacking was significantly less than those achieved by MI-E. In addition, the FVC produced by MI-E was greater than the insufflation capacity produced by breath stacking. Also, the air flows generated by MI-E more closely reflected the flow volume and velocities of normal coughing than those generated by breath stacking[173]. However, these publications have a very small number of patients with ALS. ALS is different from other neuromuscular diseases due to its rapidly progressive course, increasing disability over a very short period and survival of only 2-3 years from symptom onset. Such a disease poses the question of increasing survival in the face of disability and poor quality of life. In 1999, the American Academy of Neurology issued practice parameters for the care of patients with ALS[58]. These parameters suggested that MI-E could be used as an option to clear airway secretions. However, the evidence base for the MI-E was thought to be inconclusive and based on expert opinion, retrospective analysis and small case series. No controlled trial for MI-E was identified.

Sancho *et al.* studied the efficacy of MI-E in 26 ALS patients (15 with severe bulbar disease) in a prospective trial. They concluded that MI-E was able to generate clinically effective PCF of > 2.7 L/s in all ALS patients except for those with severe bulbar dysfunction (MIC ≤ FVC)[174]. However in this study patients with severe respiratory muscle weakness were excluded. In a similar study Chatwin *et al.* carried out a physiological assessments of 22 patients with neuromuscular disease against 19 age-matched controls[158]. Peak cough flow was measured following different cough augmentation techniques. MI-E produced the greatest increase in peak cough flow. However, this was an observational study and did not include any patients with motor neurone disease and patients with moderate to severe bulbar involvement were excluded from the study. The same author studied standard chest physiotherapy plus MI-E against standard physiotherapy without MI-E in neuromuscular patients with acute respiratory tract infections. They concluded that the airway clearance sessions were shorter in patients provided with MI-E, but both methods had similar efficacy[175]. Moreover, patients using MI-E reported a higher feeling of fatigue. Both these studies included only patients with

childhood neuromuscular diseases. Mustafa et al. reported that MI-E increased PCF by 17% in healthy controls, 26% in bulbar MND patients and 28% in non-bulbar MND patients[176].

Bento *et al.* reported an observational study involving 21 neuromuscular disease patients of which 15 had MND (6 patients with severe bulbar dysfunction at the beginning)[177]. The patients on mechanical ventilation were prescribed MI-E when assisted PCF dropped below 270 l/min. The non-bulbar patients had previously used the breath stacking technique. Patients either used MI-E either daily on a prophylactic basis or intermittently with oximetry feedback. Domiciliary MI-E therapy was well tolerated by the patients and no complications reported. Patients reported better airway clearance of secretions. During the course of follow up, visit to the emergency department was prevented in 8 patients where application of MI-E reverted the episodes of desaturation and normalized SpO_2. In 4 patients hospitalization was required to treat airway mucus encumbrance. 10 patients progressed to severe bulbar disease and tracheostomy was indicated, but only 5 accepted to undergo tracheostomy. The patients with tracheostomy continued to use MI-E. The number of chest infections treated in the community was not reported by the authors. Lack of a control group is an obvious deficiency in this study.

Winck et al. studied the physiologic effect of MI-E on the PCF and respiratory inductance plethysmography (RIP) in a prospective clinical trial including 13 patients with ALS (10 with severe bulbar disease), 9 patients with severe chronic obstructive pulmonary disease and 7 patients with other neuromuscular disorders. They concluded that MI-E was well tolerated and significantly improved PCF and oxygen saturation. There were no other changes in RIP parameters. Even in bulbar patients, peak expiratory flow to mean expiratory flow ratio (PEFMF) significantly increased suggesting decreased pharyngeal resistance. This is in contrast to the suggestion by Sancho *et al.* that in some patients with bulbar disease MI-E may be ineffective due to the dynamic collapse of the upper airway[174]. No barotraumas or other respiratory complications were reported and a pressure of 40 to -40 cm H_2O was considered to be both comfortable and effective for the patients. Gomez-Merino *et al.,* using a lung model, found that insufflation and exsufflation pressures of 35 to -35 cmH_2O or 40 to -40 cm H_2O are effective in achieving higher peak cough flows and similar pressures are also recommended by the manufacturer of the MI-E (CoughAssist® user guide). As the minimum effective cough flow of 2.7 L/s was not achieved at insufflation-exsufflation pressures below

30 cm H_2O, settings below 30 to -30 cmH_2O should not be expected to be clinically effective. In fact the same has been demonstrated in animal models[178]. Fauroux recommended higher pressure settings for better efficacy especially during lower respiratory tract infections. This is because lung mechanics change during respiratory tract infections and hence MI-E settings may need to be changed[179].

Pillastrini *et al*. studied the use of MI-E in patients with high spinal cord injuries[180]. It was a short randomised controlled trial where MI-E was studied against manual respiratory kinesitherapy (which included the use of breath-stacking). Respiratory parameters were examined before and after a session with each technique. The group using MI-E showed a significant increase in FVC, FEV1 and PEF, presumably due to better clearance of airways of secretions and mucus plugs. No statistically significant difference was observed in blood gas levels or oxygen saturation. The authors concluded that MI-E can be helpful in reducing the number of broncoscopies, the need for tracheostomy and in allowing early discharge from hospital. Furthermore when used in the community, hospital admissions can be prevented. Sancho *et al.* studied the preference of MI-E vs. tracheal suctioning in patients with ALS having tracheostomy stoma[181]. They concluded that oxygen saturation and the work of breathing performed by the ventilator significantly improved with MI-E. 72% of the patients reported MI-E to be more effective than suctioning and MI-E was more comfortable, less tiring and less irritating. MI-E is logically superior to tracheostomy suctioning as MI-E can clear medium and small bronchi and both left and right bronchi equally, in addition to the central airways. A patient and provider satisfaction survey in patients with spinal cord injuries found that patients preferred MI-E to endotracheal suctioning as a means of removing respiratory secretions[182].

Vitacca *et al.* studied the benefits of on-demand MI-E in 12 patients with ALS in a prospective study. All study participants were established on mechanical ventilators and treated in the community. MI-E was made available at home when indicated for a chest infection and to correct oxygen desaturation of < 95%. Adjustment of the ventilator and provision of assisted coughing allowed correction of SpO_2 in all the study participants and 30/47 episodes of respiratory exacerbation were treated in the community. However, there was no control group in the study and also a comparison with a programme where access to MI-E was continuous for prophylactic use (as opposed to on demand) is required.

In a study involving post-operative patients, MI-E allowed reduced need to resort to bronchoscopy to remove airway debris following chest and abdominal surgery, prevented intubation and allowed early extubation in the post-operative period[183].

Systematic review of the use of MI-E shows that evidence for the use of MI-E is evolving. It had been demonstrated that MI-E was able to increase peak cough flow and to enable effective secretion removal without resorting to invasive airway suctioning. It has been suggested that neuromuscular patients could potentially be maintained and supported at home during acute episodes of respiratory infection, possibly eliminating the need for acute admission to hospital. For patients with limited life expectancy an episode in hospital because of a chest infection can be very distressing. Although the above mentioned observational studies have confirmed safety and efficacy and there is clinical experience of several decades, the use of MI-E has not been systematically incorporated into the care of patients with MND. The CoughAssist® device has received the European conformity mark, indicating compliance with the European Union safety standards and has become widely available in Europe but is not funded within the UK National Health Service (NHS) for patients with MND. In the absence of prospective evidence, derived from well-designed randomised controlled trials, hurdles may remain in the funding for this device within the NHS.

MI-E may be ineffective for patients with severe bulbar dysfunction. With the progression of bulbar dysfunction, the upper airway collapses during expiration and then during inspiration rendering MI-E ineffective. In this situation, the patient is at high risk of aspiration leading to pneumonia and respiratory failure and tracheostomy may be advised for secretion management[184].

Few complications have been reported with the use of MI-E. Those reported include nausea, gastroesophgeal reflux, abdominal distension and discomfort. The blood pressure increases slightly (mean 8 mmHg in systole and 4 mmHg in diastole) and the pulse can increase or decrease with in-exsufflation. Pneumothorax has been rarely reported in the literature[185]. MI-E should be prescribed with caution in individuals with a history of bullous emphysema, known susceptibility to pneumothorax or pneumo-mediastinum, or a recent barotrauma.

1.17) Aims and outline of the thesis

1. Despite the benefits of NIV, respiratory complications remain the commonest cause of morbidity and mortality in MND patients. The main aim of this thesis is to investigate the role of cough augmentation techniques, particularly mechanical In-Exsufflator and the breath-stacking technique, in the management of respiratory morbidity in MND and its effect on quality of life and survival. Chapter 3 describes a randomised controlled clinical trial evaluating MI-E against the breath-stacking technique in patients with advanced MND, using NIV.

2. The second aim of this thesis is to examine the value of different respiratory function tests in the early detection of respiratory failure in MND. An accurate and reproducible respiratory assessment is vital in the management of MND. Currently available volitional tests have limitations, particularly in patients with bulbar dysfunction and an ideal test would be non-invasive and non-volitional with high sensitivity and specificity. Chapter 4 describes the accuracy of carbon dioxide levels recorded transcutaneously using TOSCA *500* monitor. Chapter 5 examines the value of clinical questioning, FVC, SNIP and $PtcCO_2$ in the detection of respiratory failure, when carried out at 3 monthly intervals.

3. Chapter 6 summarises the work and highlights the scope for future research.

CHAPTER 2

METHODS AND MATERIALS

2.1) Study participants

All study participants were recruited at the Sheffield Motor Neurone Disease Care and Research Centre. All patients fulfilled the El Escorial criteria for definite, probable or electro physiologically supported Amyotrophic Lateral Sclerosis (ALS). The main caregiver of the respective patient was recruited as a “carer”. Written informed consent was obtained from all patients and carers. Where a patient was unable to sign, verbal consent was obtained and the carer signed the consent form in the presence of a witness. The participants underwent assessments at baseline and then at three, six, nine and twelve months.

2.2) Measures of respiratory function

2.2.1) Spirometry

A volumetric spirometer (vitalograph® – Alpha) was used to record slow vital capacity (VC). A face mask was used for the patients not able to achieve a tight mouth seal. The spirometer was calibrated daily. The author, a respiratory physiologist or a trained nurse performed the spirometry. The best of three attempts was recorded.

2.2.2) Peak cough flow

The peak cough flow was recorded using a Mini-Wright Peak Flow Meter. The subjects forcefully coughed into the face mask attached to the peak flow meter. The maximum cough flow recordable with Mini-Wright peak flow meter is 700 L/minute. As for spirometry, the best of three attempts was recorded.

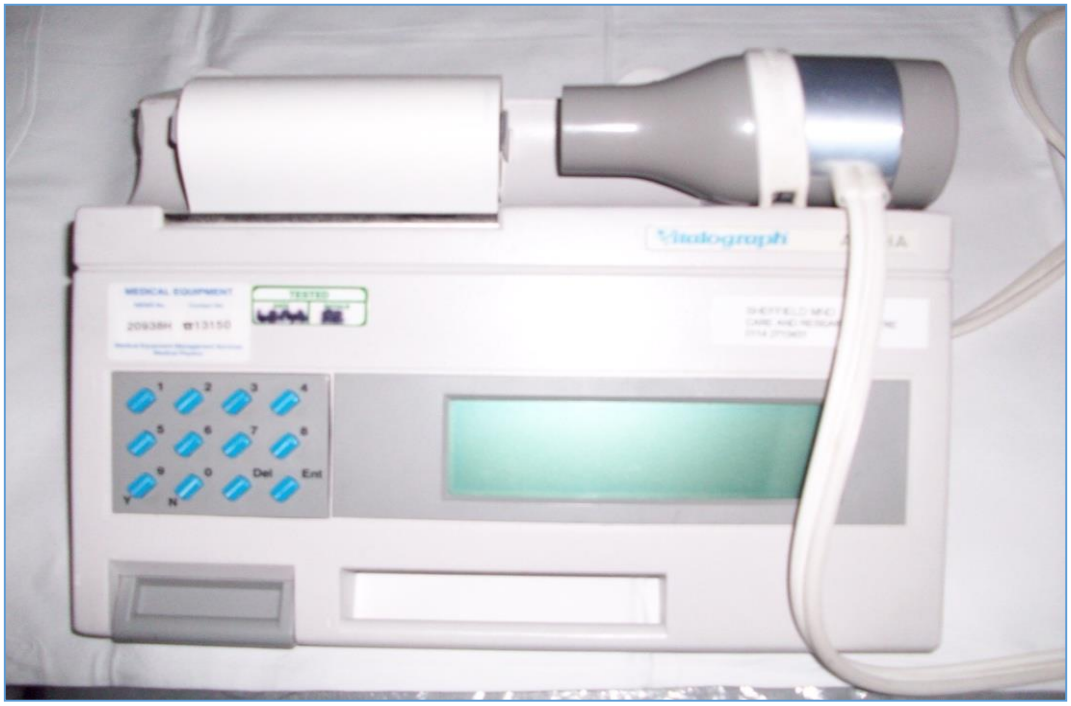


Figure 6: volumetric spirometer (vitalograph® – Alpha)

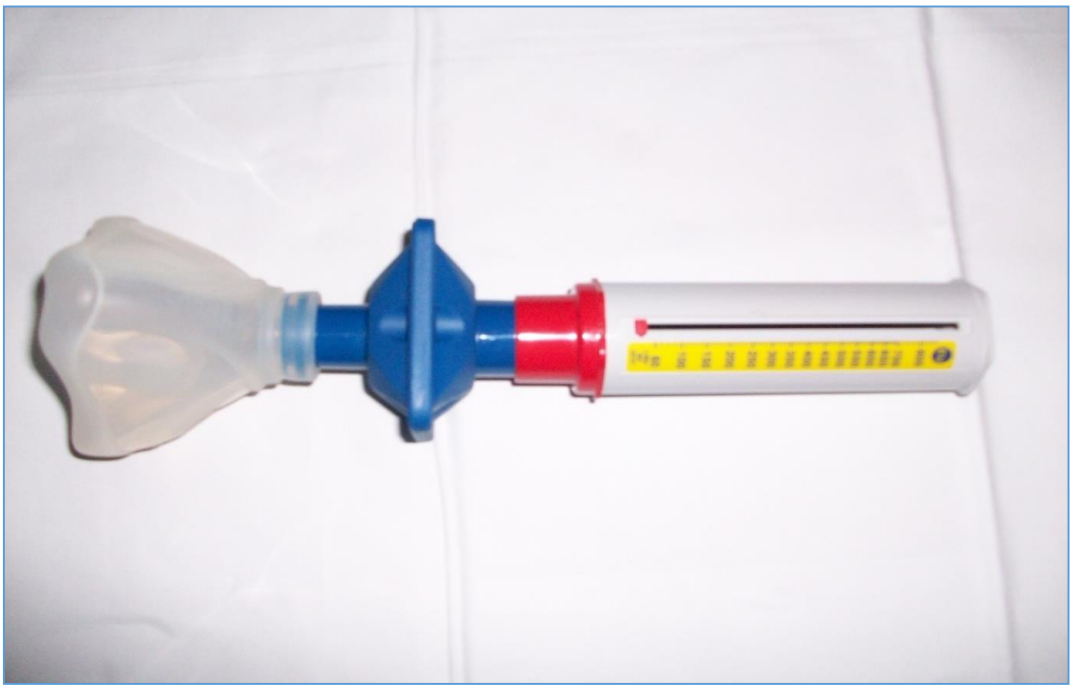


Figure 7: Mini-Wright Peak Flow Meter – used to evaluate peak cough flow

2.2.3) Arterialised ear lobe capillary blood gas analysis

The gold standard for blood gas analysis is using arterial blood samples, which provides detailed analysis of the acid–base status of the patient. An acceptably accurate alternative is the capillary blood gas analysis[186]. This method has been reported to be less painful and can be safely done by para-medical staff. There is a strong correlation and limits of agreement between arterial and arterialized blood samples with respect to pH and $PaCO_2$[187]. Hence capillary blood gas analysis was used for the body of work described in chapter 5 as a less painful alternative. A heat rub cream was applied to the ear lobe for 10-15 minutes to allow vasodilatation and arterialization of the ear lobe capillary bed. The ear lobe was then pierced with a spring loaded needle and blood collected in a capillary tube. The blood sample was analysed by a Radiometer ABL 700 blood gas analyzer without delay.

2.2.4) Transcutaneous carbon dioxide monitor (TOSCA *500*)

TOSCA *500* (Linde Medical Sensors) is a lightweight portable device which can measure PCO_2 and oxygen saturation (SpO_2) with a single sensor attached to the ear lobe. Another advantage of TOSCA is that it can provide a continuous real-time reading, allowing overnight monitoring of PCO_2 and SpO_2 to detect nocturnal hypercapnia and oxygen desaturations. The recorded patient data can be downloaded to a computer. It incorporates the physiological principle that CO_2 gas is able to diffuse through the skin and can be detected by a sensor at the skin surface. The TOSCA *500* was used in the studies to measure PCO_2 and SpO_2. Moreover, TOSCA *500* was used where overnight oximetry was carried out to determine the presence and extent of nocturnal respiratory failure. The monitor was operated in accordance with the manufacturer's operating manual. A disposable ear clip was used to attach the sensor from the TOSCA monitor to the ear lobe. Contact gel was applied between the sensor and the skin to facilitate diffusion. The device was operated on a "QUICKSTART" mode which warms the sensor to a temperature of 42°C (increasing the arterial blood supply in the dermal capillary bed below the sensor) and gives the reading in 10-15 minutes.

2.3) Measurement of bulbar function

Bulbar function is a prognostic factor in MND and may directly affect the reliability of respiratory function tests. Bulbar function was assessed using the three components of ALS functional rating scale relevant to bulbar function (i.e. Speech, Salivation and Swallowing, each scored on a scale of 0-4). Patients with an overall bulbar score of 7 - 12 were regarded as having good or mildly impaired bulbar function while patients with a score of 0 - 6 were categorised as having moderate or severely impaired bulbar function.

2.4) Monitoring disease progression

I. **Revised ALS functional rating scale (ALSFRS-R):** ALSFRS-R was used to functionally evaluate the severity and progression of MND. ALSFRS-R is a disease specific functional rating scale that provides information about bulbar function, disability and respiratory function of MND patients in a single scale (Appendix 1). It has 12 functional domains, each rated on a scale of 0-4, yielding a maximum score of 48 points. The rate of decline in the ALSFRS score mirrors disease progression and predicts overall survival[188,189]. The scale is easy to use, has been validated and has been demonstrated to show high inter-rater and intra-rater reliability[190]. Moreover, it can be reliably administered to the patients' carers if the patients themselves are unable to give the information. Also, the change in the score correlates well with the changes in isometric muscle strength and pulmonary function[191 192]. ALSFRS-R scores also correlate well with quality of life scores as measured by the Sickness Impact Profile, indicating that functional ability is a strong determinant of quality of life in ALS[191]. However, the respiratory subscale of the ALSFRS-R correlates less well with the forced vital capacity (FVC). The ALSFRS-R has been used in several recent clinical trials of medicinal products to assess disease progression in patients with MND.

   Other, ALS rating scales include Norris ALS scale, Appel ALS scale and Hillel ALS severity scale.[193-195] They have the disadvantage of mixing both impairment and disability measures together in one scale.

II. **Manual muscle strength testing:** In addition to functional assessments, manual muscle strength testing (MMT) using the Medical Research Council scale was used as a measure of disease progression. To avoid inter-rater variability most of the manual muscle scoring was carried out by the author. MMT lacks precision and is also dependent on patient-examiner factors. Other more objective methods include isokinetic (fixed force gauges) and hand-held dynamometers.[196,197] Fixed force gauges require is time consuming and requires cumbersome equipment. Hand-held dynamometers allow easy bedside assessment of muscle strength and according to the published literature repeated muscle strength scores do not vary by more than 15%[198]. As the author did not have experience in using this technique and also considering the patients' welfare, MMT was considered sufficient for the purpose of this study.

III. **Weight (nutritional status):** MND patients are at increased risk of malnutrition due to dysphagia, difficulty with feeding, anorexia and higher metabolic rate. Nutritional status at the time of diagnosis is an independent prognostic factor and malnutrition over the course of disease is associated with shortened survival[199]. One study reported a 34% increased risk of death with every 5% decrease in usual weight during follow up[200]. Malnourished patients had a 2.15 increased relative risk of death compared to patients with normal BMI. A reduced risk of death was observed in overweight and obese patients. Consequently weight loss can be used as a marker of disease progression. Body weight was recorded where possible at each clinic attendance of participating patients.

2.5) Health related quality of life measurements

Quality of life for people with MND is influenced by a number of factors, including disability and psychological health. It is widely reported that psychosocial, supportive and spiritual factors, rather than physical factors, play a larger role in mediating quality of life in MND[201]. Although quality of life is not a measure of disease progression, it is important to assess QoL in clinical trials of therapeutic interventions. QoL issues are important for regulatory bodies such as the National institute for Clinical Excellence. It is well established that NIV improves QoL in ALS[125] hence we evaluated the effects of cough augmentation techniques on QoL as well (Chapter 3). For this purpose, an instrument should be reproducible, be able to detect

inter-subject differences and be responsive to both disease progression and treatment. It has been suggested that physiological measures cannot be used to predict QoL, and QoL should be measured directly. The following instruments have been used for the body of work described in chapter 3.

I. **Short Form - 36:** SF - 36 is a widely used generic (as opposed to disease specific) self-completed questionnaire to assess health related QoL. It can be used in a variety of diseases and hence has the advantage of enabling comparison of the relative burden of different diseases and comparing health benefits produced by different treatment interventions. Although it is designed to measure all important aspects of quality of life, it does not take into account specific issues affecting QoL in MND. It contains 36 items over 8 domains of health: physical functioning; role limitation due to physical problems; social functioning; mental health; energy/vitality; bodily pain; and overall health perception. The results are summarized as the psychometrically based Physical Component Summary (PCS) and the Mental Component Summary (MCS). There is no single overall score. It has been proven to be valid, reliable (internally consistent and reproducible) and responsive to both disease progression and treatment with NIV in MND[128,202]. In a disease such as MND, we expect the MCS to be most responsive to the intervention as with the relentless progression of neuromuscular weakness, decline in PCS is inevitable.

II. **Sleep Apnoea Quality of Life Index (SAQLI):** It has been shown that the sleep related symptoms have the greatest response to NIV[203]. To measure this effect SAQLI can be used. SAQLI was initially developed for use in patients with obstructive sleep apnoea[204]. It has been shown that the components specifically assessing respiratory and sleep-related problems have greater discriminatory power with respect to disease severity and responsiveness to treatment with NIV than generic instruments. However, SAQLI has a disadvantage of moderate non-response rates to certain items when administered to subjects early in the disease without symptoms of respiratory compromise[203] and it has to be administered by an interviewer. In chapter 3 as the participants have established respiratory failure and are receiving treatment with NIV,

SAQLI is a useful tool to assess treatment effects. It has strong content and construct validity and is responsive to changes in quality of life[205].

2.6) Assessment of the carer's burden

Patients with MND are often worried about dependency issues and stress on the spouse/carer. Moreover, there is evidence to suggest that caregivers influence the physical and mental health of MND patients[206]. The Caregiver Strain Index (CSI) is a well-established questionnaire, designed to quantify the strain levels amongst carers of patients with long-term illnesses. It enquires about various aspects of the life of the carer like sleep, personal plans, and finances, physical and mental strain. CSI has been used in MND[207]. Thirteen aspects are tested and affirmative responses are recorded. A score of seven or above indicates an increased level of stress. The CSI is used in the body of work described in chapter 3 to assess the quality of life of the main carer of the patient and the impact of the treatment on the carer.

2.7) Criteria for initiating NIV

The National Institute for Health and Clinical Excellence (NICE) has published a guideline on the use of NIV in patients with MND[208]. The guideline recommends that respiratory assessment should occur at or near the time of initial diagnosis of MND and repeated at 3 monthly intervals. Given its relative ease of use, measurement of oxygen saturation (SpO_2) is proposed as the first line screening tool, along with enquiry about sleep related symptoms. SpO_2 measurement is supplemented by tests of respiratory function such as Forced Vital Capacity (FVC), Sniff Nasal Inspiratory Pressure (SNIP) or Maximal Inspiratory mouth Pressure (MIP). The interval can be altered according to patients' symptoms, signs and rate of disease progression. In chapter 3, patients were selected for NIV if they met two of the following criteria:

- Symptoms of hypersomnolence or non-refreshing sleep
- Orthopnoea due to the diaphragmatic weakness
- FVC < 60% predicted
- Nocturnal or day time hypercapnia (PCO_2 > 6.0 kPa)

In cases where there was uncertainty, nocturnal oximetry was carried out and NIV offered if average PCO_2 > 6.0 kPa or SpO_2 < 88% for 5 consecutive minutes during sleep. The first trial of NIV was carried out at as an inpatient in the department of Neurology at the Royal Hallamshire Hospital. The inspiratory and expiratory airway pressures were titrated based on tolerability, symptoms and morning blood gases. The patients were offered a range of interfaces to select the most comfortable interface. A humidifier was added to the NIV equipment for patients complaining of excessive airway dryness.

One of the major concerns with NIV is safe use in patients with severe bulbar weakness. In such patients there is a risk that secretions may be blown down an unprotected airway into the trachea and lower airways. In a randomized controlled trial of NIV, the bulbar patient group treated with NIV exhibited a non-significant trend to worse survival[125]. However in another study, an improvement in survival in bulbar patients was seen, if they were hypercapnic at initiation of NIV[131]. Our practice is to offer a trial of NIV to patients with severe bulbar disease, with proper attention to management of secretions and an appropriate interface.

The patients who were able to use NIV for four or more hours a night were considered to be successfully established on treatment. The “Cough Assist study” was discussed with the patients two weeks following the initiation of NIV.

2.8) Cough augmentation techniques

Chapter 3 describes a randomised controlled clinical trial evaluating the role of cough assist devices in the management of respiratory morbidity in MND. In this trial a mechanical in-exsufflator device is evaluated against breath stacking technique with a manual insufflator. The use of these devices and background literature is discussed in chapter 1.

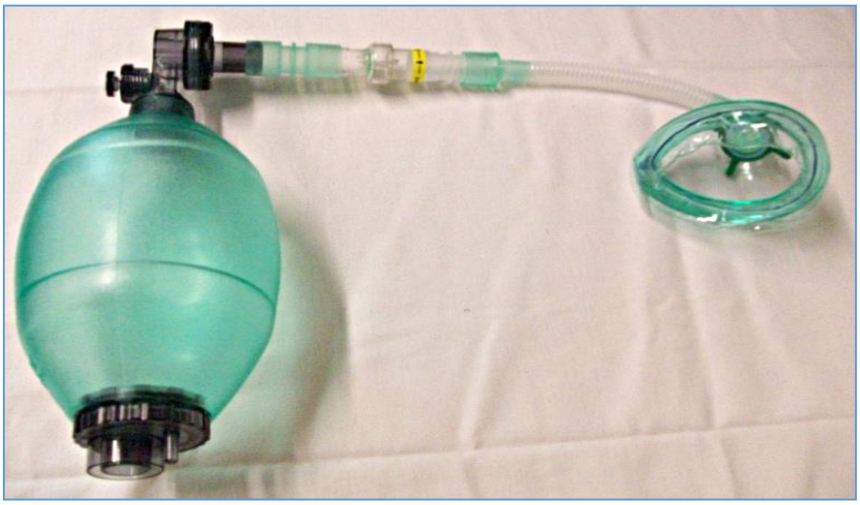


Figure 8: AMBU bag system with face mask used for breath stacking

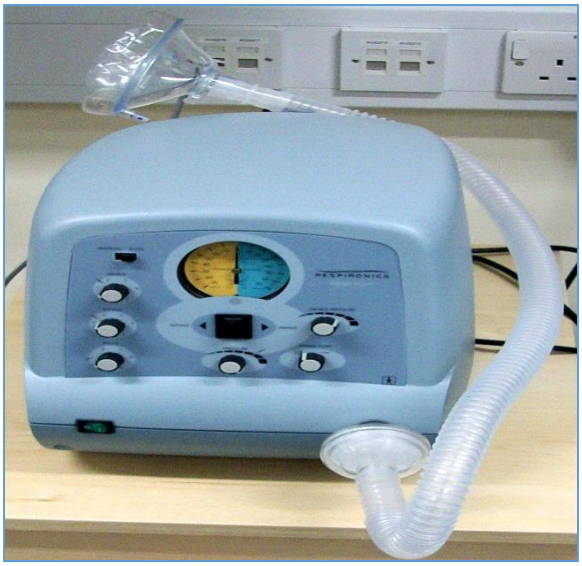


Figure 9: CoughAssist® Mechanical In-Exsufflator (Philips Respironics)

2.9) Recording the compliance

A diary was used to track compliance with the cough assist devices. The participants were asked to document their use of MI-E or breath-stacking, any symptoms of respiratory tract infection (a comprehensive list of these symptoms is provided within the diary), contacts made with the GP due to respiratory problems, use of antibiotics and any hospital admissions.

2.10) Blinding in the randomised trial

Blinding in randomised clinical trials improves validity. However, as this trial was a PhD work it was important for me to carry out assessments and data collection, while also interviewing the participants for their experience of using their respective cough augmentation devices. Hence I could not be blinded. Use of clinical judgement was required when deciding upon the number of episodes of chest infection and the duration of chest infections. This carries the risk of introducing the researcher's bias. Under ideal circumstances, effect of an intervention should be analysed by a blinded researcher. However, this was not possible in this trial due to the reasons described above and due to lack of man power.

2.11) Power calculation

The primary outcome measure for this study is number of days with symptoms of chest infection requiring antibiotic therapy, whether in hospital or in the community. A sample size of 10 in each group will have 80% power to detect a 6.667 fold change in means (e.g. 20 vs. 3 days of chest infection per year), assuming that the coefficient of variation (standard deviation divided by mean) is 2.500 using a two group t-test with a 0.050 two-sided significance level. We added a safety margin to ensure adequate power in case of loss of some patients during follow-up and hence will include 20 patients in each group. This power calculation is extrapolated based on the evidence in the literature regarding days of hospitalization with chest infections for patients with MND using NIV (mean of 20±41 days for patients with NIV alone versus around 1.4±4 for patients with NIV plus CoughAssist®)[83].

The power for a survival analysis (to demonstrate a 20% improvement in predicted survival with 80% power) would be insufficient with the number of patients available. Based on the information in the literature on median survival of MND patients established on NIV (234 days) the sample size required for 80% power to detect a 20% improvement in survival is over

500 patients per group. This was not feasible with the resources available and hence only an exploratory secondary analysis will be done for survival.

2.12) Statistical analysis

Statistical analysis was performed using SPSS version 10 (SPSS, Chicago, 11., USA) and STATA. All outcome measures were analysed on an intention to treat basis and all tests of significance were two-sided. Unpaired Student's t-test was used for univariate comparison of group subjects' continuous variables. A non-parametric test; Mann-Whitney U test was used for non-parametric data. Kaplan and Meier survival curves were used for survival times. A Cox regression model was used to assess, and adjust for, the effect of different baseline measures on survival.

In the quality of life analysis, the duration that quality of life remained above 75% of the baseline value over the 12 month follow-up was compared using analysis of covariance.

CHAPTER 3

MECHANICALLY ASSISTED COUGH IN MOTOR NEURONE DISEASE: A RANDOMISED TRIAL

3.1) Research question

Does the use of a Mechanical In-Exsufflator (MI-E) improve pulmonary morbidity, quality of life and survival in patients with motor neurone disease (MND) using non-invasive ventilation (NIV)?

3.2) Research Hypothesis

The routine use of MI-E by patients with MND using NIV will improve pulmonary compliance, reduce hospital admissions due to chest infections and improve their day-to-day management of respiratory secretions.

3.3) Aims of the Study

This study aims to determine whether routine use of MI-E by patients with MND using NIV reduces respiratory morbidity and mortality (number of chest infections, hospitalization and deaths due to respiratory problems), improves quality of life, and survival.

In the UK MI-E is not currently routinely available for domiciliary use for patients with MND. A well designed study is required to determine whether MI-E is of benefit to patients with MND established on NIV. Such evidence is required in order to convince health care commissioners to allow funding for the provision of MI-E devices on a more comprehensive basis. This study is designed with the aim of generating such evidence.

3.4) Study design

This is a prospective randomised controlled clinical trial of the domiciliary use of mechanical in-exsufflator versus manual insufflators (MI) in patients with MND using NIV. Patients with familial or sporadic MND (diagnosed according to the El Escorial criteria) who are established on NIV were randomized to receive either MI-E, or MI, via a computer generated process of minimisation which ensured a balance of prognostic factors between the two groups[209]. A cohort of 40 MND patients was recruited and followed-up for at least 12 months or until death. The participants were given a diary to record their compliance with the study device

and the number of days with symptoms of chest infection, treated with antibiotics in the community or in hospital.

3.5) Study participants

a) Inclusion criteria:

1. The patient should not have any serious medical problems, apart from MND, which may reduce their life expectancy.
2. The patient should be capable of giving informed consent and should not have evidence of any significant impairment of cognitive function.
3. Patients with MND in respiratory failure meeting 2 of the following criteria indicating the need for NIV:
    - Nocturnal or daytime hypercapnia (ABG's $PaCO_2$ > 6.0 kPa)
    - Nocturnal hypoxaemia (SaO_2 < 88% for 5 consecutive minutes during sleep)
    - Lung function tests - FVC <60%predicted
    - Maximal expiratory pressure <60cm H_2O
    - Orthopnoea
    - Symptoms of hypersomnolence or non-refreshing sleep
4. The patient should have a main carer who is willing to assist the patient in following the study regimen.
5. The patient must fulfill the El Escorial criteria for definite ALS, clinically probable ALS, or clinically probable laboratory-supported ALS.

b) Exclusion criteria:

1. Inability to tolerate NIV.
2. Use of MI-E contra-indicated (a history of bullous emphysema, susceptibility to pneumothorax or pneumo-mediastinum, or recent barotrauma).
3. The presence of a significant medical condition, other than MND, which may reduce life expectancy.
4. The presence of significant impairment of cognitive function (for example fronto-temporal dysfunction which is clinically evident and noticeable to the family).

5. Participation in any other respiratory interventional trial.

3.6) Outcome measures

a) Primary outcome measure: The number of days with symptoms of chest infection requiring antibiotic therapy, whether in the hospital or in the community.

b) Secondary outcome measures:

i. the number of days hospitalized due to chest infection
ii. Quality of life
iii. Survival
iv. Impact on the primary carer
v. Respiratory function (FVC, PCF, SpO_2, $PaCO_2$)

3.7) Ethics and governance

This study was reviewed and approved by the South Sheffield Research Ethics committee (Ref. no. 08/H1313/83). It was registered with the research and development department of Sheffield Teaching Hospitals NHS Trust (Ref. STH15161) and has been undertaken in accordance with the research governance regulations.

3.8) Results

A total of 42 patients were recruited. The following flow chart illustrates different phases of the study (Figure 10).

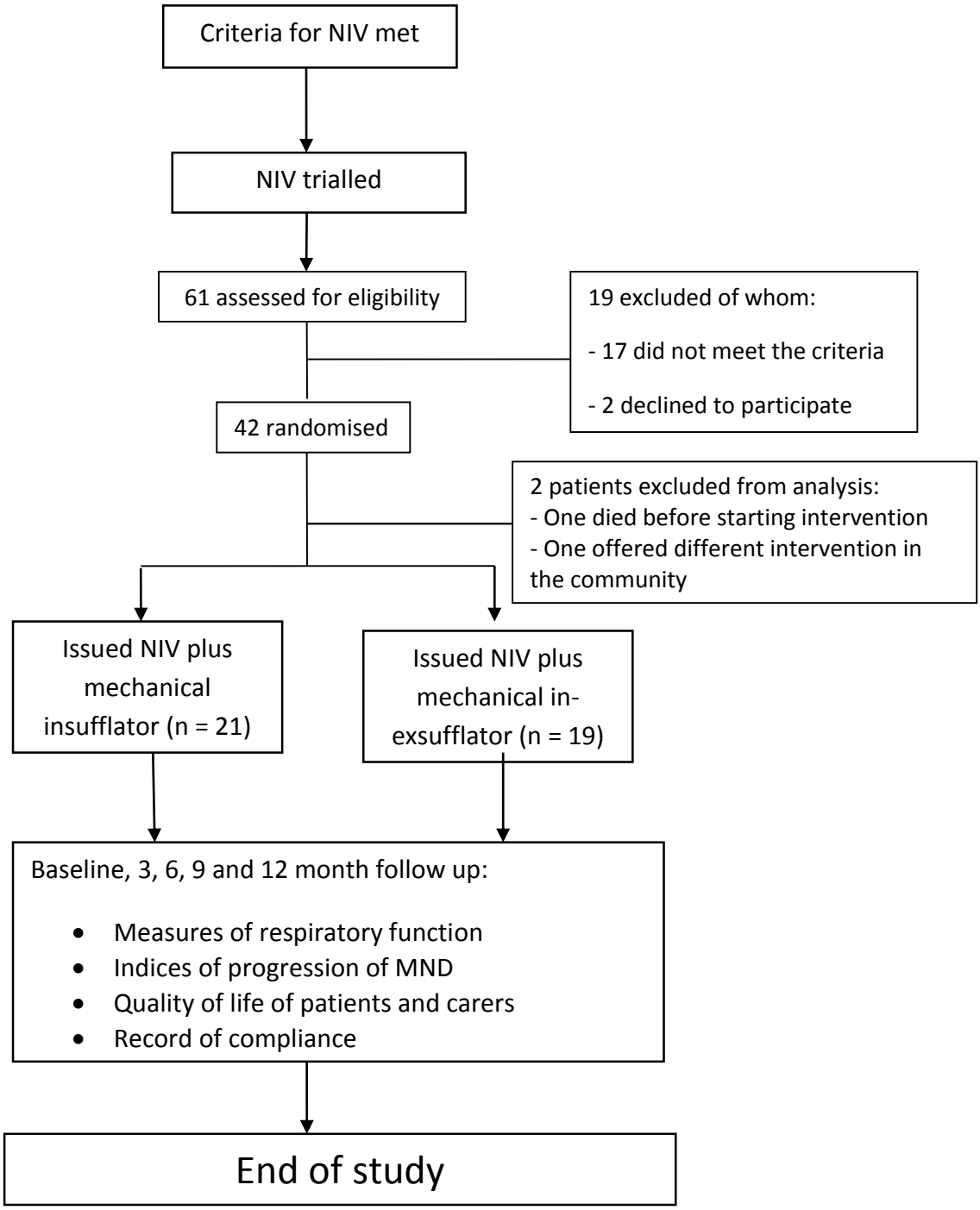


Figure 10: CONSORT flow chart of the progress through the phases of the study

3.8.1) Baseline characteristics of the study participants

Table 4 summarises the baseline characteristics of the study participants. The difference between individual characteristics were statistically insignificant, except for PCF (p=0.008). Prognostic factors taken into account for randomisation included slow vital capacity (SVC), age, gender and body mass index (BMI).

Table 4: Comparison of baseline characteristics of the study participants

Parameter	**Breath stacking**	**MI-E (CA)**
Total number	21	19
Mean Age (years)	64.1 [10.5]	60.2 [15.2]
Number (%) of females	4 females (19%)	3 females (16%)
Mean duration of the Disease (months)*	30.8	33.6
Site of onset: • Limb onset • Bulbar onset • Respiratory onset	 15 (71%) 5 (24%) 1 (5%)	 13 (68%) 6 (32%) 0
Mean BMI (Kg/m^2)	24.2 [5.6]	22.3 [17.4]
Mean SVC (% predicted)	57.6 [20.2]	49.2 [22.6]
Mean PCF (L/min)*	221.1	144.3
Mean Bulbar Score • No. with normal to moderate bulbar impairment (score 7-12) • No. with severe bulbar impairment (score 0-6)	7.9 13 (62%) 8 (38%)	8.2 13 (68%) 6 (32%)
ALSFRS-R	27.5	28.2
MRC Muscle Score	87.5	87.3

*Duration from the onset of symptoms to enrolment.
[] – Standard deviation
MI-E – Mechanical in-exsufflator (CoughAssist®)
BMI – Body mass index
SVC – slow vital capacity
ALSFRS-R – ALS functional rating scale revised
MRC – medical research council
*p = 0.008

3.8.2) Compliance

Table 5 & 6 illustrate the compliance of the study participants with NIV and their respective study intervention. Compliance was categorised as “regular use” if intervention used at least once per day on at least 5 days per week, “low use” if the intervention used when needed, and “non-use” if intervention was used any less. The usage was recorded in a patient diary. The average daily use ranged from 0 to 10.5 times in the MI-E arm and 0 to 4 times in the breath- stacking arm.

Table 5: Characteristics of the participants – Breath-stacking arm

ID	Gender	Age	Level of use	Reason for low or non-use	Site of onset	ALSFRS Bulbar sub score* 0=severe impairment 12=normal	ALSFRS Limb sub score** 0=severe impairment 12=normal
P1	Female	60+	Non-user	Too tired	Bulbar	2	8
P2	Female	70+	Non-user	Unable to stack breaths	Bulbar	2	0
P3	Male	40+	Low user		Limb	5	10
P4	Male	60+	Non-user	Unable to stack breaths	Bulbar	5	7
P5	Male	60+	Died early	Stroke leading to early death	Limb	12	12
P6	Female	60+	Regular user		Limb	12	7
P7	Male	60+	Regular user		Limb	12	9
P8	Male	70+	Regular user		Limb	3	6
P9	Female	60+	Regular user		Bulbar	8	10
P10	Male	70	Died early	Fall leading to early death	Limb	9	5
P11	Male	60+	Regular user		Respiratory	9	10
P12	Male	60+	Low user	Excessive secretions	Bulbar	0	8
P13	Male	50+	Regular user		limb	11	6
P14	Male	70+	Regular user		Limb	10	6
P15	Male	40+	Non-user	No perceived need	Limb	9	7
P16	Male	60+	Regular user		Limb	12	8
P17	Male	80+	Regular user		Bulbar	3	9
P18	Male	50+	Regular user		Limb	12	11
P19	Male	60+	Non-user	Poor inspiratory effort	Limb	5	8
P20	Male	60+	Regular user		Limb	12	9
P21	Male	40+	Regular user		Limb	12	11
	M=17 F=4	Mean age = 64 yrs.	Regular=12 Low=2 Non-user=5 Died early=2		Limb=14 Bulbar =6 Respiratory=1		

*Composite of speech, saliva and swallowing scores **Composite of handwriting, feeding and dressing/hygiene scores

Table 6: Characteristics of the participants – MI-E arm

ID	Gender	Age	Level of use	Reason for low or non-use	Site of onset	ALSFRS Bulbar sub score* 0=severe impairment 12=normal	ALSFRS Limb sub score** 0=severe impairment 12=normal
P1	Male	50+	Regular user		Limb	8	8
P2	Male	40+	Non-user	Claustrophobia	Limb	1	0
P3	Female	50+	Low user	Excessive saliva	Bulbar	0	10
P4	Male	60+	Regular user		Limb	12	7
P5	Male	60+	Regular user		Limb	11	7
P6	Male	50+	Low user	Intolerant to pressure	Limb	10	9
P7	Male	50+	Low user	Intolerant to pressure	Bulbar	4	4
P8	Female	20+	Regular user		Limb	12	6
P9	Male	70+	Died early		Bulbar	4	10
P10	Male	60+	Low user	Intolerant to pressure	Bulbar	1	5
P11	Male	70+	Regular user		Limb	12	10
P12	Male	60+	Non-user	Generates cough	Limb	12	8
P13	Male	70+	Regular user		Limb	12	6
P14	Male	70+	Low user	Ineffective	Limb	9	6
P15	Male	70+	Died early		Limb	12	7
P16	Male	20+	Non-user	No perceived need	Limb	12	8
P17	Female	70+	Non-user	Intolerant to pressure	Bulbar	3	9
P18	Male	60+	Regular user		Limb	10	11
P19	Male	70+	Regular user		Limb	10	8
	M=16 F=3	Mean age = 60 yrs.	Regular=8 Low=5 Non-user=4 Died early=2		Limb=14 Bulbar =5 Respiratory=0		
*Composite of speech, saliva and swallowing scores **Composite of handwriting, feeding and dressing/hygiene scores							

3.8.3) Mortality

As expected in an MND population, chronic respiratory failure was the commonest cause of death. Inability to tolerate NIV and chest infections (due to airway mucus accumulation or aspiration of saliva) were common factors contributing to shortened survival. No mortality was related to the intervention. Table 7 summarises the causes of death amongst the study participants. At the time of writing 6 participants are alive (median survival 757 days) in the breath-stacking group and 5 participants are alive (median survival 1045 days) in the MI-E group.

Table 7: Causes of death in the study participants

Breath-stacking group (15 deaths)		MI-E group (14 deaths)	
ID	**Cause of death**	**ID**	**Cause of death**
2	End stage disease	4	Acute-on-chronic respiratory failure due to aspiration (poor compliance with NIV & MI-E due to severe bulbar disease)
3	End stage disease	7	Recurrent aspiration, poor tolerance of NIV (due to severe bulbar disease), acute-on-chronic respiratory failure due to bibasal pneumonia. Died in hospital
5	Acute-on-chronic respiratory failure due to chest infection. Died in the hospital	12	End stage disease, mask fell off during sleep
6	End stage disease	14	Chronic respiratory failure/poor compliance with NIV
8	Stroke	15	End stage disease
9	End stage disease	19	Chronic respiratory failure
11	End stage disease	20	Chronic respiratory failure, poor compliance with NIV (due to severe bulbar disease)
18	Heart attack (had obesity, complicated diabetes and rheumatoid arthritis)	23	Chronic respiratory failure, poor compliance with NIV
21	Severe fall	24	Chronic respiratory failure, poor compliance with NIV
22	Chronic respiratory failure (respiratory onset disease)	30	Acute-on-chronic respiratory failure due to chest infection. Died in hospital
26	Chronic respiratory failure, poor compliance with NIV (due to severe bulbar disease). Fall and head injury might have contributed to death	33	Acute-on-chronic respiratory failure due to chest infection. Died in hospital
29	Chronic respiratory failure, poor compliance with NIV	37	Chronic respiratory failure
32	Chronic respiratory failure	38	Chronic respiratory failure
36	Chronic respiratory failure	41	Chronic respiratory failure
39	Chronic respiratory failure, poor compliance with NIV		

3.8.4) Profile of pulmonary morbidity over the period of follow-up

Table 8 and Figures 11-13 summarise the parameters of pulmonary morbidity in the two groups. No statistically significant difference has been demonstrated between the two groups. Table 9 outlines the details of pulmonary morbidity at each of the follow-up time points.

Table 8: Pulmonary morbidity

parameter	Measure	Breath-stacking group (n = 21, f/u days = 5941)	MI-E group (n = 19, f/u days = 4491)	p value
Number of chest infection requiring antibiotics	Number of patients with any chest infection	7 (33%)	6 (32%)	0.91
	Total number of chest infections	13 [1.11]	19 [1.91]	0.87
	Mean chest infection (range)	0.62 (0-4)	1 (0-6)	0.45
	Median chest infection	0	0	0.87
	Mean per month per patient	0.10	0.13	0.75
	Median per month	0	0	0.87
Number of days with symptom requiring antibiotics	Total number of days with symptoms requiring antibiotics	90 [8.52]	95 [14.89]	0.85
	Mean (range)	4.28 (0 – 33)	5 (0 – 65)	0.85
	Median	0	0	0.78
	Mean per month	0.45	0.63	
	Median per month	0	0	0.83
	Mean duration of symptoms per chest infection	**6.9**	**3.9**	**0.16**
Number of hospitalizations due to chest infections	Number of patients with any hospitalization	5 (24%)	4 (21%)	0.84
	Total number of hospitalizations	6 [0.56]	6 [0.67]	0.87
	Mean hospitalization (range)	0.28 (0 – 2)	0.31 (0 – 2)	0.88
	Median hospitalization	0	0	0.93
	Mean hospitalization per month	0.06	0.07	0.81
	Median hospitalization per month	0	0	0.93
	Chance of hospitalization	**0.46**	**0.31**	**0.47**

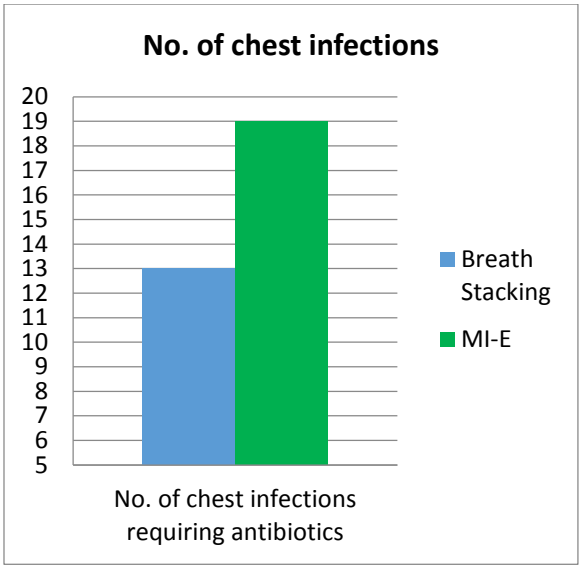


Figure 11: Bar chart to illustrate the number of chest infections

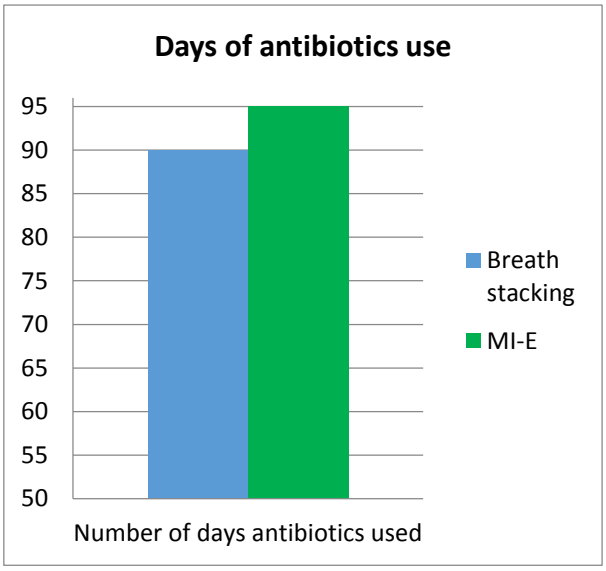


Figure 12: Bar chart to illustrate the number of days of antibiotic use

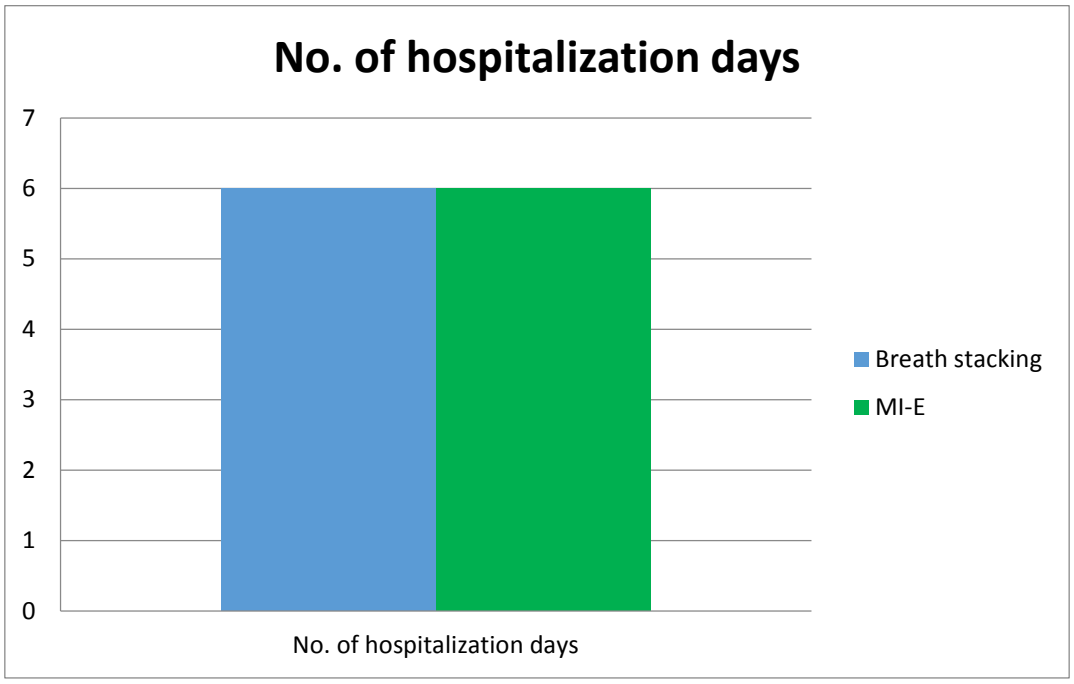


Figure 13: Bar chart to illustrate total number of hospitalization days in the two groups

Table 9: Pulmonary morbidity at each follow-up time points

Measure	Time (month)	Breath-stacking group		MI-E group	
Number of chest infection requiring antibiotics		No of pts. at follow up	Total number	No of pts. at follow up	Total Number
	0-3	21	7	19	10
	3-6	17	4	15	1
	6-9	15	2	11	3
	9-12	13	0	8	5
	Total/12m		**13**		**19**
Number of days with symptom requiring antibiotics	0-3	21	38	19	37
	3-6	17	38	15	12
	6-9	15	14	11	20
	9-12	12	0	8	26
	Total/12m		**90**		**95**
Number of hospitalizations	0-3	21	2	19	3
	3-6	17	2	15	1
	6-9	15	1	11	1
	9-12	12	1	8	1
	Total/12m		**6**		**6**

3.8.5) Profile of pulmonary morbidity in relation to bulbar function

Tables 10 and 11 summarise the parameters of pulmonary morbidity of the two groups in relation to their bulbar function. Bulbar function was assessed using the three components of ALSFRS-R relevant to bulbar function (i.e. Speech, Salivation and Swallowing, each scored on a scale of 0-4). A score of 7-12 was considered as normal to moderate bulbar impairment while a score of 0-6 suggested severe bulbar impairment. Table 11 and 12 outline the detail of pulmonary morbidity for good-moderately impaired and severely impaired bulbar function respectively, at each follow-up time points. Table 14 summarises the number of participants who suffered pulmonary morbidity in each group. Table 15 compares the pulmonary morbidity within each group when sub-classified by the severity of bulbar dysfunction.

Table 10: Pulmonary morbidity in patients with good - moderately impaired bulbar function

parameter	Measure	Breath-stacking group (n = 13, f/u days = 3919)	MI-E group (n = 13, f/u days = 3555)	p value
Number of chest infection requiring antibiotics	Number of patients with any chest infection	3 (23%)	3 (23%)	
	Total number of chest infections	5 [0.86]	9 [1.7]	0.56
	Mean chest infection (range)	0.38 (0-3)	0.69 (0-6)	
	Median chest infection	0	0	
	Mean per month	0.03	0.07	
	Median per month	0	0	
Number of days with symptom requiring antibiotics	Total number of days with symptoms requiring antibiotics	52 [9.4]	70 [17.9]	0.80
	Mean (range)	4 (0 – 33)	5.3 (0 – 65)	
	Median	0	0	
	Mean per month	0.39	0.59	
	Median per month	0	0	
	Mean duration of symptoms per chest infection	10.4	7.7	
Number of hospitalizations due to chest infections	Number of patients with any hospitalization	1 (7.6%)	2 (15.3%)	
	Total number of hospitalizations	2 [0.56]	3 [0.59]	0.73
	Mean hospitalization (range)	0.15 (0 – 2)	0.23 (0 – 2)	
	Median hospitalization	0	0	
	Mean hospitalization per month	0.01	0.02	
	Median hospitalization per month	0	0	
	Chance of hospitalization	0.4	0.33	

Table 11: Pulmonary morbidity in patients with severely impaired bulbar function

Parameter	Measure	Breath-stacking Patients (n = 8, f/u days = 2022)	MI-E group (n = 6, f/u days = 936)	p value
No. of chest infection requiring antibiotics	No. of pts. with any chest infection	4 (50%)	3 (50%)	
	Total number of chest infections	8 [1.41]	10 [2.33]	0.51
	Mean chest infection (range)	1 (0-4)	1.6 (0-6)	
	Median chest infection	0.5	1	
	Mean per month	0.11	0.32	
	Median per month	0	0	
No. of days with symptom requiring antibiotics	Total number of days with symptoms requiring antibiotics	38 [7.3]	25 [4.9]	0.85
	Mean (range)	4.75(0 – 21)	4.1 (0 – 12)	
	Median	1	3	
	Mean per month	0.56	0.80	
	Median per month	0	0	
	Mean duration of symptoms per chest infection	**4.75**	**2.5**	
No. of hospitalizations due to chest infections	No. of pts. with any hospitalization	4 (50%)	2 (33%)	
	Total number of hospitalizations	4 [0.53]	3 [0.83]	0.87
	Mean hospitalization (range)	0.5 (0 – 1)	0.5 (0 – 2)	
	Median hospitalization	0.5	0	
	Mean hospitalization per month	0.05	0.06	
	Median hospitalization per month	0	0	
	Chance of hospitalization	**0.5**	**0.3**	

Table 12: Pulmonary morbidity at each follow-up time point in patients with good - moderately impaired bulbar function

Parameter	**Months**	**Good bulbar function (n = 26)**			
		No. of pts.	BS (n = 13)	No. of pts.	MI-E (n = 13)
Number of Chest infections	0-3	13	3	13	4
	3-6	10	1	11	1
	6-9	10	1	9	3
	9-12	7	0	6	1
	Tot/12 m		**5**		**9**
Number of days with symptoms requiring antibiotics	0-3	13	26	13	21
	3-6	10	16	11	12
	6-9	10	10	9	20
	9-12	7	0	6	17
	Tot/12 m		**52**		**70**
Number of hospital admissions	0-3	13	1	13	2
	3-6	10	1	11	0
	6-9	10	0	9	1
	9-12	7	0	6	0
	Tot/12 m		**2**		**3**

Table 13: Pulmonary morbidity at each follow-up time point in patients with severely impaired bulbar function

Parameter	**Months**	**Poor bulbar function (n= 14)**			
		No. of pts.	BS (n = 8)	No. of pts.	MI-E (n = 6)
Number of Chest infections	0-3	8	4	6	6
	3-6	7	3	4	0
	6-9	5	1	2	0
	9-12	3	0	1	4
	Tot/12 m		**8**		**10**
Number of days with symptoms requiring antibiotics	0-3	8	12	6	16
	3-6	7	22	4	0
	6-9	5	4	2	0
	9-12	3	0	1	9
	Tot/12 m		**38**		**25**
Number of hospital admissions	0-3	8	1	6	1
	3-6	7	1	4	1
	6-9	5	1	2	0
	9-12	3	1	1	1
	Tot/12 m		**4**		**3**

Table 14: Number of participants who experienced pulmonary morbidity

Parameter	Months	Breath-stacking group	MI-E group
Number (%) of patients with any chest infection	0-3	6 (28.5%)	5 (26.3%)
	3-6	3 (17.6%)	1 (6.6%)
	6-9	2 (13.3%)	2 (18.1%)
	9-12	0 (0%)	2 (25%)
Number (%) of patients who used antibiotics	0-3	6 (28.5%)	5 (26.3%)
	3-6	3 (17.6%)	1 (6.6%)
	6-9	2 (13.3%)	2 (18.1%)
	9-12	0 (0%)	2 (25%)
Number (%) of patients who required hospital admission	0-3	2 (9.5%)	2 (10.5%)
	3-6	2 (11.7%)	1 (6.6%)
	6-9	1 (6.6%)	1 (9.0%)
	9-12	1 (8.3%)	1 (12.5%)

Table 15: Pulmonary morbidity by bulbar function within each group

	Breath-stacking group			Mechanical in-exsufflator group		
Parameter	**Good bulbar function (n= 13)**	**Poor bulbar function (n= 8)**	**P value**	**Good bulbar function (n= 13)**	**Poor bulbar function (n= 6)**	**P value**
Number of pts. with any chest infection	3 (23%)	4 (50%)	0.15	3 (23%)	3 (50%)	0.15
Number of Chest infections	5	8	0.22	9	10	0.31
Number of days with symptoms requiring antibiotics	52	38	0.85	70	25	0.87
Mean duration of symptoms per chest infection	10	4.56	0.02	4.9	2.8	0.52
Number of hospital admissions	2	4	0.17	3	3	0.43
Chance of hospitalization	0.4	0.5		0.33	0.30	

3.8.6) Quality of life indices over the period of follow-up

Table 16 summarises the quality of life (QoL) indices during the period of follow-up in the two groups. The duration that a QoL domain remained above 75% of the baseline is presented. Tables 17 and 18 summarise the domains of quality of life in the two groups in relation to their bulbar functions.

In a progressive disease like MND, the domains considered most responsive to the interventions were SF 36 mental component summary (MCS) and sleep apnoea quality of life index symptoms domain (sym)[125]. Patients in breath-stacking group had longer median duration that MCS, SF 36 energy vitality and sym were maintained above 75% of baseline. For SF 36 role emotional, social function, mental health, and pain the difference was almost similar with a marginally better general health perception in MI-E group. However, these small observed differences did not reach statistical significance.

Tables 19-21 illustrate time-weighted mean improvement in QoL domains above baseline with negative values indicating deterioration below baseline. As above, higher but statistically insignificant improvement in the MCS was observed in the breath-stacking group. There was however, no improvement in sym in the breath-stacking group and insignificant improvement was observed in MI-E group. There was significantly less decline in the physical component summary of the SF-36 in the MI-E group ($p = 0.003$).

Table 16: Median duration (range) that quality of life measures were maintained above 75% of baseline

Measure	Breath stacking (n=21) Domain > 75% of baseline in days (range)	MI-E (n=19) Domain > 75% of baseline in days(range)	P value
SF 36 physical function	114.5 (0-419)	205 (0-400)	0.57
SF 36 role physical	0 (0-367)	95 (0-357)	0.74
SF 36 role emotional	209.5 (0-367)	190.74 (0-405)	0.69
SF 36 social function	186.5 (0-378)	190.74 (0-405)	0.52
SF 36 mental health	271 (0-398)	266 (0-405)	0.37
SF 36 energy vitality	330 (0-419)	266 (0-405)	0.19
SF 36 pain	252 (0-369)	205 (0-405)	0.73
SF 36 general health perception	196.02 (0-398)	205 (0-405)	0.55
SF 36 physical component summary	95.75 (0-419)	133 (0-405)	0.62
SF 36 mental component summary	**329 (0-398)**	**205 (0-443)**	**0.41**
SAQLI daily function	199 (0-267)	190.74 (0-405)	0.77
SAQLI social interactions	271 (0-398)	205 (0-405)	0.58
SAQLI emotional function	271 (0-398)	205 (0-405)	0.74
SAQLI symptoms	**279.75 (0-398)**	**205 (0-443)**	**0.59**
SAQLI score	271 (0-398)	205 (0-405)	0.54

Table 17: Median duration (range) that quality of life measures were maintained above 75% of baseline in patients with good - moderately impaired bulbar function

Measure	Breath stacking (n=13) Domain > 75% of baseline In days (range)	MI-E (n=13) Domain > 75% of baseline In days (range)	P value
SF 36 physical function	135.5 (0-419)	280 (0-400)	0.28
SF 36 role physical	104.75 (0-367)	133 (0-357)	0.66
SF 36 role emotional	209.5 (0-367)	266 (0-405)	0.69
SF 36 social function	209.5 (0-378)	266 (0-405)	0.81
SF 36 mental health	329 (0-383)	280 (0-405)	0.71
SF 36 energy vitality	336 (0-419)	280 (0-405)	0.38
SF 36 pain	252 (0-369)	277.5 (0-405)	0.88
SF 36 general health perception	246.7 (0-388)	267.7 (0-405)	0.87
SF 36 physical component summary	98.01 (0-419)	133 (0-405)	0.73
SAQLI daily function	253.5 (0-367)	266 (0-405)	0.91
SAQLI social interactions	273 (0-369)	280 (0-405)	0.98
SAQLI emotional function	275.25 (0-369)	289 (0-405)	0.86
SAQLI symptoms	283.5 (0-383)	280 (0-443)	0.85
SAQLI score	314.25 (0-383)	280 (0-443)	0.78

Table 18: Median duration (range) that quality of life measures were maintained above 75% of baseline in patients with severely impaired bulbar function

Measure	Breath stacking (n=8) Domain > 75% of baseline in days (range)	MI-E (n=6) Domain > 75% of baseline in days (range)	P value
SF 36 physical function	57.25 (0-398)	53.79 (0-205)	0.45
SF 36 role physical	0 (0-298.5)	0 (0-215.16)	0.67
SF 36 role emotional	161.1 (0-366)	0(0-326)	0.21
SF 36 social function	158 (0-398)	0(0-326)	0.34
SF 36 mental health	168 (0-398)	0(0-326)	0.22
SF 36 energy vitality	240 (0-398	69 (0-326)	0.23
SF 36 pain	197.1 (0-366)	69 (0-326)	0.40
SF 36 general health perception	132.79 (0-398)	69 (0-326)	0.39
SF 36 physical component summary	0 (0-398)	69 (0-326)	0.72
SAQLI daily function	136.75 (0-366)	69 (0-215.16)	0.49
SAQLI social interactions	199.25 (0-398)	69 (0-326)	0.27
SAQLI emotional function	181 (0-398)	69 (0-215.16)	0.31
SAQLI symptoms	197.12 (0-398)	69 (0-326)	0.40
SAQLI score	181 (0-398)	69 (0-326)	0.40

Table 19: Time-weighted mean improvement in QoL domains above baseline (negative values indicate deterioration below baseline)

Measure	Breath stacking (n=21) Time-weighted mean improvement in QoL domains	MI-E (n=19) Time-weighted mean improvement in QoL domains	P value
SF 36 physical function	-12 (-96 – 3)	-7.5 (-42 – 0)	0.07
SF 36 role physical	-0.75 (-25.5 – 22.5)	1.5 (-4.5 – 27)	0.08
SF 36 role emotional	-0.75 (-28.5 – 16.5)	0 (-4.5 – 28.5)	0.17
SF 36 social function	-6 (-30 – 19.5)	-4.5 (-22.5 – 48)	0.03
SF 36 mental health	0.75 (-28.5 – 25.5)	-9 (-31.5 – 16.5)	0.20
SF 36 energy vitality	-6 (-19.5 – 16.5)	0 (-33 – 58.5)	0.34
SF 36 pain	-7.1(-30 – 39)	-1.5 (-8.25 – 51)	0.10
SF 36 general health perception	-3.3 (-58.2 – 46.5)	-4.5 (-38.1 – 54)	0.96
SF 36 physical component summary	-31.9 (-155 – 36.3)	-9.6 (-86.8 – 128.8)	0.003
SF 36 mental component summary	**4.15 (-123.5 – 59.6)**	**-5.31 (-46 – 182)**	**0.32**
SAQLI daily function	-15.37 (-114 – 37.5)	0 (-64 – 85.5)	0.17
SAQLI social interactions	-11.25 (-70.5 – 22.5)	-4.5 (-34.5 – 43.5)	0.17
SAQLI emotional function	-4.5 (-75 – 13.5)	4.5 (-58 – 31.5)	0.14
SAQLI symptoms	**-3 (-81 – 70.5)**	**9 (-12.7 – 85.5)**	**0.22**
SAQLI score	-1.8 (-18 – 9.4)	0.32 (-4 – 16)	0.11

Table 20: Time-weighted mean improvement in QoL domains above baseline in patients with good - moderately impaired bulbar function

Measure	**Breath stacking (n=13) Time-weighted mean improvement in QoL domains**	**MI-E (n=13) Time-weighted mean improvement in QoL domains**	**P value**
SF 36 physical function	-25.5 (-94.5 – 0)	-7.5 (-42 - 0)	0.07
SF 36 role physical	-3 (-25.5 – 22.5)	9 (0 – 27)	0.13
SF 36 role emotional	-4.5 (-28.5 – 11.25)	0 (0-28.5)	0.11
SF 36 social function	-6 (-30 – 19.5)	1.5 (-22.5 – 48)	0.09
SF 36 mental health	-1.5 (-28.5 – 25.5)	-7.5 (-31.5 – 16.5)	0.48
SF 36 energy vitality	-6 (-19.5 – 16.5)	0 (-33 – 58.5)	0.43
SF 36 pain	-10.5 (-27 – 39)	0 (-15 – 51)	0.14
SF 36 general health perception	-3.75 (-58.2 - 52.5)	0 (-38.1 – 54)	0.92
SF 36 physical component summary	-34.2 (-106.23 – 36.3)	-2.36 (-86.8 – 128.8)	0.02
SF 36 mental component summary	**10.96 (-123.5 – 59.6)**	**-1.66 (-62.7 – 182)**	**0.20**
SAQLI daily function	0 (-114 – 37.5)	9 (-64.5 – 85.5)	0.31
SAQLI social interactions	-13.5 (-70.5 – 22.5)	-4.5 (-34.5 – 43.5)	0.30
SAQLI emotional function	-4.5 (-49.5 – 13.5)	15 (-58.5 – 31.5)	0.06
SAQLI symptoms	**3 (-81 – 70.5)**	**15 (-10.5 – 85.5)**	**0.41**
SAQLI score	-0.42 (-18.4 – 9.4)	0.42 (-4 – 16)	0.20

Table 21: Time-weighted mean improvement in QoL domains above baseline in patients with severely impaired bulbar function

Measure	**Breath stacking (n=8) Time-weighted mean improvement in QoL domains**	**MI-E (n=6) Time-weighted mean improvement in QoL domains**	**P value**
SF 36 physical function	-10.5 (-96 – 3)	-8.2.5 (-22.5 – 0)	0.40
SF 36 role physical	0 (-42 – 13.5)	0 (-4.5 – 15)	0.51
SF 36 role emotional	0 (-27 – 6.75)	0 (-4.5 – 16.5)	0.80
SF 36 social function	-6 (-24 –0)	-4.5 (-6 – 7.5)	0.17
SF 36 mental health	3 (-25.5 – 3)	-9.75 (-14.25 – -3)	0.25
SF 36 energy vitality	-6 (-19.5 – 16.5)	1.5 (-11.25 – 9)	0.61
SF 36 pain	-4.5 (-10.5 – 6)	-3.75 (-4.5 – 15)	0.55
SF 36 general health perception	-3 (-43.5 – 46.5)	-4.5 (-4.5 – -0.3)	0.80
SF 36 physical component summary	-25.9 (-155 – -10)	-11 (-19 – 17)	0.13
SF 36 mental component summary	**-0.3 (-72 – 56)**	**-17 (-33.6 – 73)**	**0.85**
SAQLI daily function	-21 (-52.5 – 6)	-6 (-36 – 0)	0.44
SAQLI social interactions	-4.5 (-33 – 1.5)	-1.5 (-12.75 – 1.5)	0.21
SAQLI emotional function	**0 (-10.5 – 15)**	**-9 (-15 -0)**	**0.21**
SAQLI symptoms	**-10.5 (-19.5 – 18)**	**6 (-12.7 – 24)**	**0.28**
SAQLI score	-3.4 (-6.8 – 2.4)	-1.1 (-3.5 – 0.85)	0.43

3.8.7) Indices of disease progression over the period of follow-up

Table 22 summarises the indices of disease progression over the period of follow up. Figures 14 and 15 illustrate the trend of SVC and PCF in the two groups, while Figures 16 and 17 illustrate the trends for ALSFRS and MMS respectively. The average per month decline in SVC was 0·94% in the breath-stacking group and 0·45% in the MI-E group (p=0·47). The PCF declined on average by 5·77 L/min/month in the breath-stacking group and improved by 0·9 L/min/month in the MI-E group (p=0·43). Tables 23 and 24 summarise the indices of disease progression in the two groups in relation to their bulbar functions.

Table 22: Indices of disease progression

Measure	Time (month)	Breath-stacking group		MI-E group		P value
% SVC		No.	Mean (SD)	No.	Mean (SD)	
	0	20 [1]	57.6 (20.2)	19	49.15 (22.57)	0.22
	3	17	52.4 (20.5)	12 [2]	51.1 (23.3)	0.88
	6	15	48 (20.2)	10 [1]	49.7 (22.75)	0.84
	9	12[1]	44 (18.2)	7 [1]	44 (27.98)	0.98
	12	9 [3]	44.3 (16.9)	6	43.66 (24.64)	0.95
PCF (L/min)	0	20 [3]	221.1 (73.39)	15 [4]	144.3 (83.51)	0.008
	3	15 [2]	173.5 (80.05)	10 [2]	209 (80.79)	0.30
	6	11 [2]	169 (55.5)	9 [2]	168.33 (56.5)	0.97
	9	12 [1]	159.7 (55.68)	5 [3]	168 (66.48)	0.79
	12	8 [2]	151.8 (36.0)	5 [1]	150 (65.19)	0.94
ALSFRS	0	21	28.76 (7.86)	19	28.15 (8.13)	0.81
	3	17	27.58 (6.82)	13	26.15 (7.62)	0.59
	6	15	25.5 (6.4)	11	24.63 (7.61)	0.74
	9	13	22.9 (5.2)	8	23.62 (8.05)	0.81
	12	12	21.0 (4.8)	6	24.16 (4.91)	0.22
MRC Muscle Score	0	20	89.9 (21.57)	19	87.3 (20.53)	0.70
	3	17	94 (14.21)	13	84.23 (16.77)	0.09
	6	14	88.14 (13.9)	10	85.1 (20.58)	0.66
	9	13	81.9 (23.3)	7	77.14 (26.51)	0.68
	12	13	76 (4.8)	6	68 (33.16)	0.55

[] No. of patients unable to perform the test

% SVC = Percentage predicted slow vital capacity

PCF = Peak Cough Flow

ALSFRS = Amyotrophic lateral sclerosis Functional rating Scale

MRC = Medical Research Council

SD = Standard Deviation

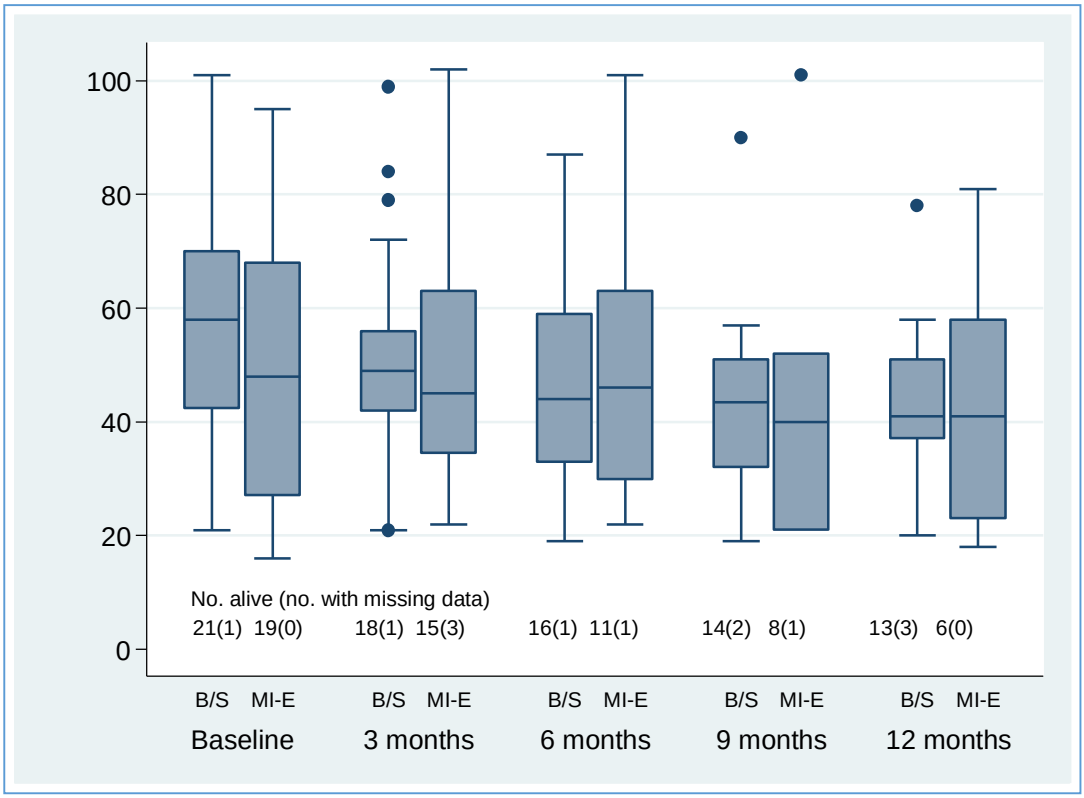


Figure 14: Serial measures of Slow Vital Capacity during the time course of the study

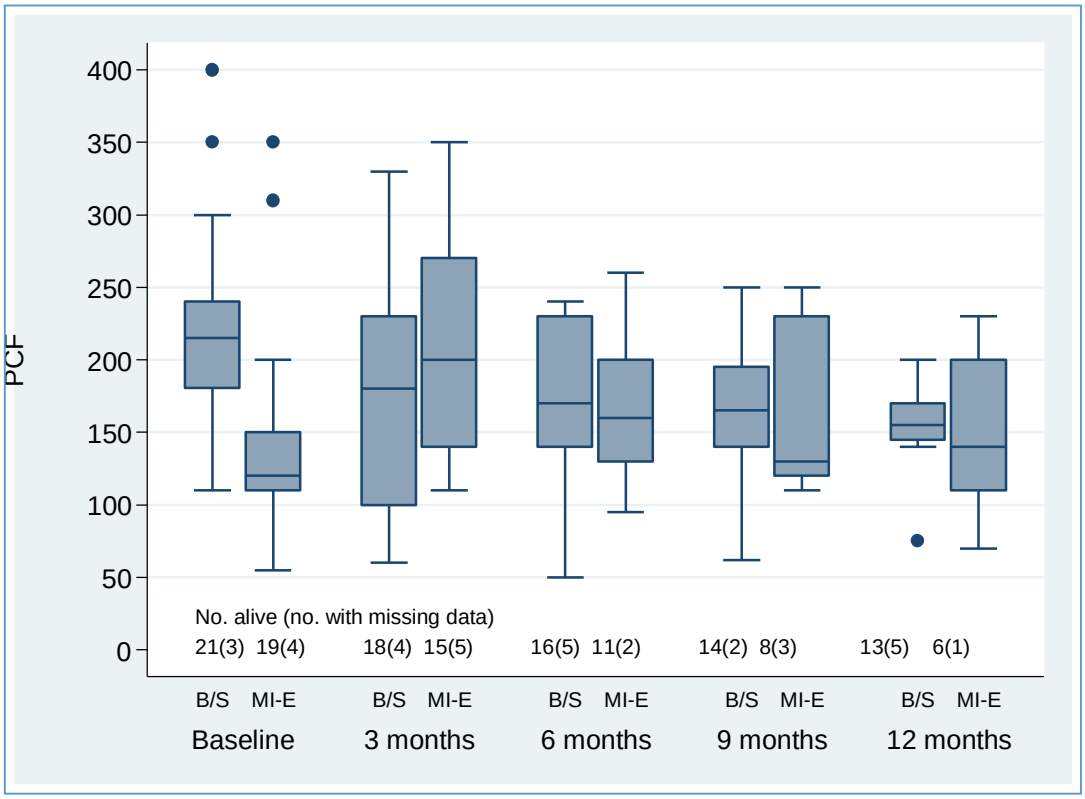


Figure 15: Serial measures of Peak Cough flow during the time course of the study (error bars are SD)

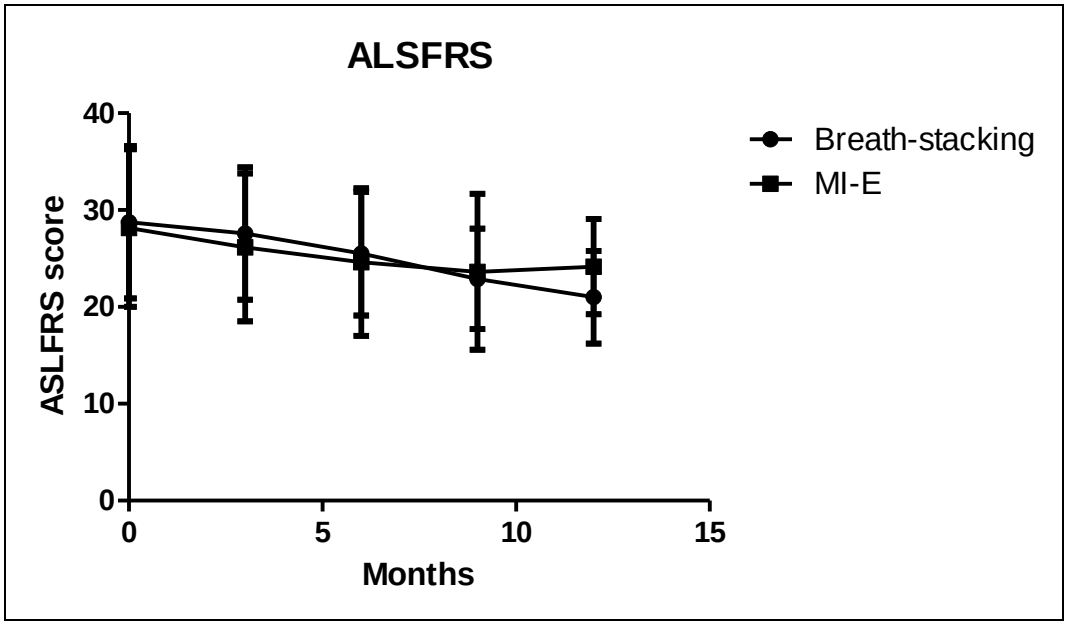


Figure 16: Serial measures of ALS Functional Rating Scale during the time course of the study (error bars are SD)

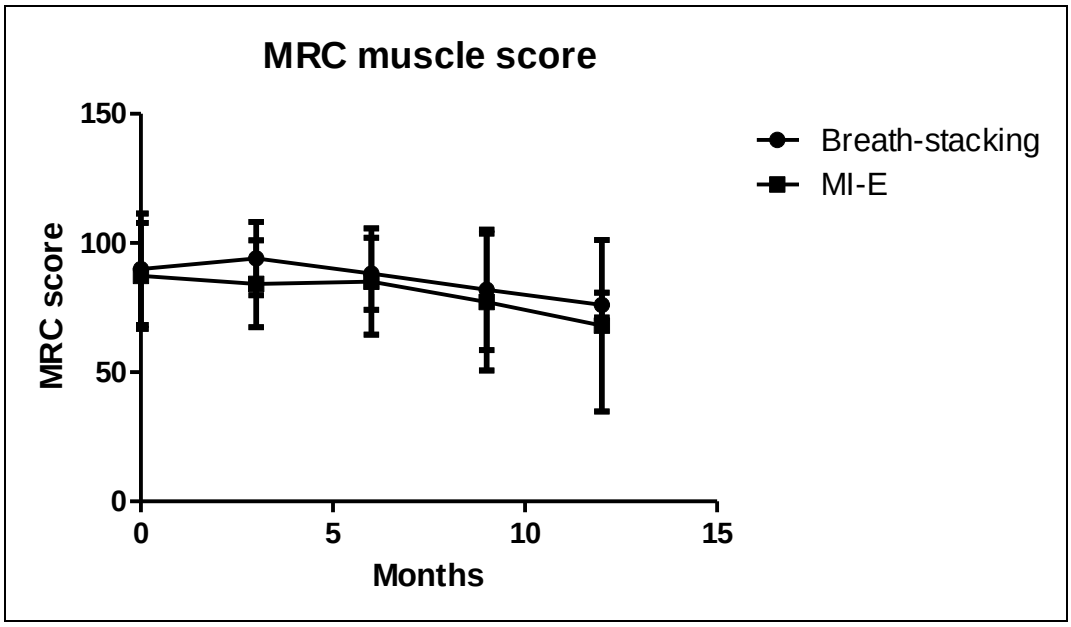


Figure 17: Serial measures of MRC Manual Muscle Score during the course of the study (error bars are SD)

Table 23: Indices of disease progression in patients with good - moderately impaired bulbar function

Measure	Time (month)	Breath stacking Patients		CoughAssist® Patients		P value
% SVC		No.	Mean (SD)	No.	Mean (SD)	
	0	13	61.30 (15.93)	13	55.38 (23.0)	0.45
	3	11	53.8 (17.9)	10	52.9 (24.0)	0.92
	6	11	48.27 (18.35)	9	50 (24.1)	0.85
	9	8 [1]	40.6 (9.6)	6	45 (30.5)	0.69
	12	7 [2]	37.4 (10.4)	6	43.6 (24.64)	0.55
PCF (L/min)	0	13	234.6 (77.20)	12 [1]	160 (86.0)	0.03
	3	10 [1]	196 (80.8)	9 [1]	207.7 (87.7)	0.76
	6	10 [1]	163 (54.5)	8 [1]	164.3 (59.12)	0.95
	9	8 [1]	174.3 (52.8)	5 [1]	168 (66.48)	0.85
	12	6 [3]	145.8 (35.8)	5 [1]	150 (65.19)	0.89
ALSFRS	0	13	31.1 95.2)	13	30.30 (7.6)	0.47
	3	11	30.6 (5.71)	10	28.8 (6.17)	0.48
	6	11	25.9 (6.9)	9	25.3 (8.15)	0.86
	9	9	23.4 (5.59)	6	24.14 (8.5)	0.84
	12	9	21.85 (4.9)	6	24.16 (4.9)	0.39
MRC Muscle Score	0	12	93.5 (13.01)	13	86.5 (21.31)	0.33
	3	11	92.54 (16.2)	10	84.7 (16.76)	0.28
	6	10	86.1 (14.5)	8	82 (22.05)	0.64
	9	9	77.3 (26.0)	6	74.6 (28.14)	0.85
	12	9	70.8 (25.7)	6	68 (33.16)	0.85

[] No. of patients unable to perform the test

% SVC = Percentage predicted slow vital capacity

PCF = Peak Cough Flow

ALSFRS = Amyotrophic lateral sclerosis Functional rating Scale

MRC = Medical Research Council

SD = Standard Deviation

Table 24: Indices of disease progression in patients with severely impaired bulbar function

Measure	Time (month)	Breath-stacking group		MI-E group	
% SVC		No.	Mean (SD)	No.	Mean (SD)
	0	7 [1]	50.71 (26.53)	6	35.66 (15.34)
	3	6	49.8 (26.41)	2 [1]	42.5 (24.78)
	6	4	47 (28.15)	1 [1]	47
	9	4	51 (30.13)	1	40
	12	3 [1]	59 (18.52)	0	--
PCF (L/min)	0	5 [3]	186 (53.66)	3 [3]	81.66 (27.53)
	3	4 [2]	117.5 (47.87)	1 [2]	220
	6	1 [3]	230	1 [1]	200
	9	4	130.5 (47.3)	[1]	--
	12	2 [2]	170 (42.42)	0	--
ALSFRS	0	8	23.25 (8.6)	6	23.5 (7.71)
	3	6	22 (5.0)	3	17.33 (5.03)
	6	4	24.5 (5.4)	2	31.5 (4.9)
	9	4	21.75 (4.99)	1	20
	12	4	19.75 (4.27)	0	--
MRC Muscle Score	0	8	84.37 (30.6)	6	89 (20.56)
	3	6	96.6 (10.4)	3	82.66 (20.50)
	6	4	93.25 (12.84)	2	97.5 (4.9)
	9	4	92.25 (13.14)	1	92
	12	4	87.5 (16.38)	0	--

[] Number of patients unable to perform the test

% SVC = Percentage predicted slow vital capacity

PCF = Peak Cough Flow

ALSFRS = Amyotrophic lateral sclerosis Functional rating Scale

MRC = Medical Research Council

SD = Standard Deviation

3.8.8) Effect on the carer

Table 25 and Figure 18 summarises carer strain index (CSI) in the two groups over the period of follow up. A score of seven or above is considered as an increased level of stress. The mean CSI in the whole study cohort ranged from 2.83-5.5, with a trend towards reduced strain in the MI-E group at the 12 month time point, though this difference did not reach statistical significance.

Table 25: Carer strain index

Measure	Time (month)	Breath-stacking Patients		MI-E group		P value
		n	Median (SD)	n	Median (SD)	
Carer strain index	0	21	4.09 (2.77)	19	5 (2.90)	0.32
	3	17	4.41 (2.39)	12	4.41 (3.28)	0.99
	6	15	4.7 (2.96)	9	4.42 (3.07)	0.69
	9	13	4.8 (2.8)	8	4.25 (3.45)	0.67
	12	13	5.5 (2.90)	6	2.83 (3.12)	0.08

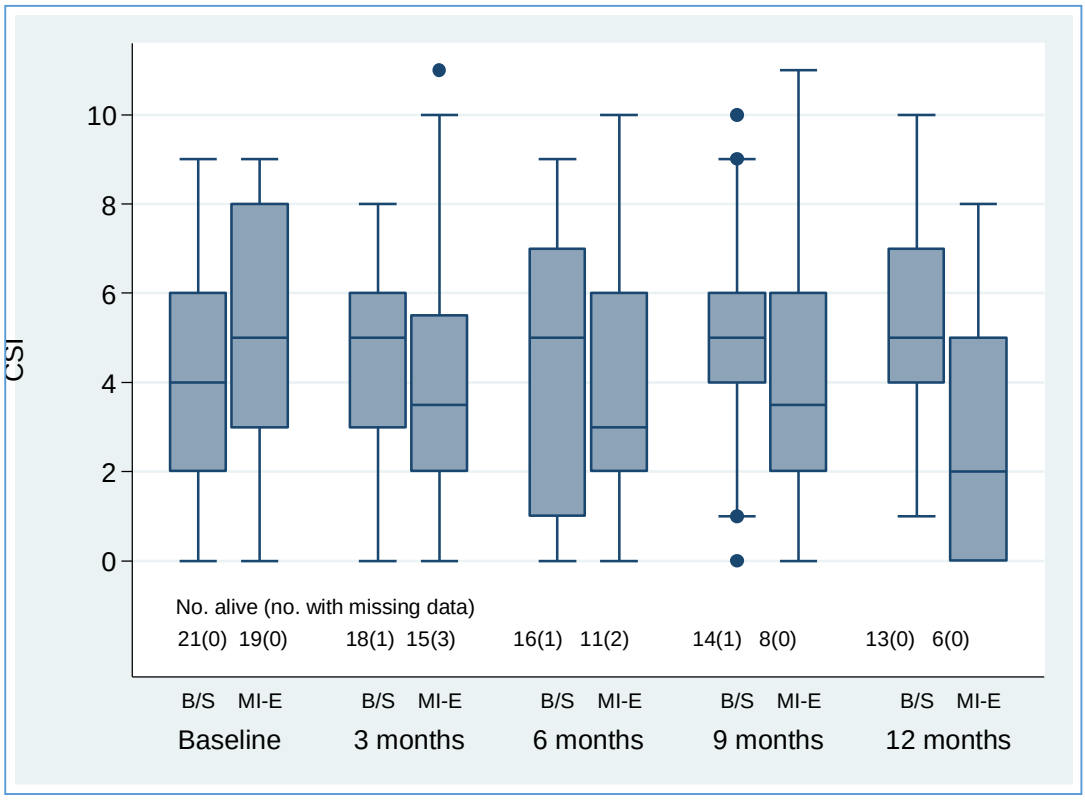


Figure 18: Serial measures of the carer strain index during the time course of the study (error bars are SD)

3.8.9) Causes of failure to use the assigned device

Table 26 summarises the causes of treatment failure in the two groups. In the breath-stacking group, three patients with severe bulbar disease (mean score 3) could not use the device due to inability to close the glottis in order to hold successive breaths. Three patients died unexpectedly due to adverse health events which include stroke, a fall and a heart attack. Two patients did not use the device because of lack of perceived need.

Four patients in the MI-E group with severe bulbar disease (mean score 3) had difficulty in tolerating the pressure of the MI-E. They used the machine at a very low pressure and could not achieve the minimal effective pressure (i.e. 30 cmH_2O). One of them had hypersialorrhea and recurrent chest infections remained a major problem in the last days of life, possibly due to aspiration of saliva. Another patient with severe bulbar disease was taken to the hospital following an episode of aspiration and underwent emergency tracheostomy. Thereafter the tracheostomy was used for secretion removal and the use of MI-E was stopped. One patient was poorly compliant with both NIV and MI-E due to claustrophobia induced by the face mask. Two patients did not use the device because of lack of perceived need. Six patients died within the first three months of entering into the study. All of these patients could not persevere with NIV, the predominant cause of which was severe bulbar dysfunction.

There were no adverse events reported in relation to the use of breath-stacking or MI-E.

Table 26: Causes of treatment failure

Causes of treatment failure	Breath-stacking group	MI-E group
Lack of interest	2	2
Lack of efficacy	0	1
Poor tolerance/inability to use	3	4
Adverse events	3 (1 Stroke, 1 Fall, 1 heart attack)	1 (emergency tracheostomy)
Early deaths (within first 3 months of entering into the trial)	3	6

3.8.10) Impact of poor bulbar function on compliance with NIV

Table 27 summarises the impact of bulbar function on compliance with NIV. Most patients in the MI-E group who had poor bulbar function were poorly compliant with NIV. However, this was not the case in breath stacking group, where six of eight patients with poor bulbar function managed to comply with NIV. In addition, three patients with good bulbar function in the MI-E group could not comply with NIV whereas only one patient with good bulbar function in breath-stacking group was poorly compliant with NIV. This is likely to contribute to the shortened overall survival in the MI-E group. Of note is that three patients in the breath-stacking group died unexpectedly due to adverse health events which included stroke, a fall and a heart attack. This suggests that the survival confounders were somewhat balanced in the two groups.

Table 27: Relationship of poor bulbar function to NIV compliance in the two groups

Breath-stacking poor bulbar patients (n=8)		MI-E poor bulbar patients (n=6)	
Bulbar score	NIV compliance	Bulbar score	NIV compliance
2	Good (≥ 8h/day)	1	Poor
2	Good (≥ 8h/day)	0	Poor
5	Good (≥ 8h/day)	4	Poor
5	Good (≥ 8h/day)	4	Moderate (4-8h/day)
3	Moderate (4-8h/day)	1	Poor
0	Poor	3	Moderate (4-8h/day)
3	Moderate (4-8h/day)		
5	Poor		

3.8.11) Adverse events

As per the principles of good clinical practice in medical research, the study participants were monitored for adverse events. Any event which adversely affected the health of the study participants was recorded. An event which required a hospitalisation or resulted in death was considered a “serious adverse event”. Table 28 lists minor adverse events, while table 29 lists serious adverse events.

Table 28: Minor adverse events

Breath-stacking group		MI-E group	
ID	**Adverse event**	**ID**	**Adverse event**
02	Chest infection 20-30th Sep., 2009	01	Chest infection 2-9th July 2009 Chest infection 26th Aug-6th Sep., 2009 Chest infection 29th Oct-9th Nov., 2009 Chest infection 13th Feb-19th Feb., 2010 Chest infection 11th Mar-18th Mar., 2010 Chest infection 12th May-31th May., 2010
05	Chest infection 13th Jan-14th Jan., 2010 Chest infection 24th Feb-26th Feb., 2010	07	Chest infection 29th Sep- 5th Oct., 2010 Chest infection 5th Oct-10th Oct., 2010 Chest infection 22nd Oct-27th Oct., 2010 Chest infection 16th Nov-21st Nov., 2010
11	Chest infection April 2011	15	Chest infection 30th Jul-2nd Aug., 2010
13	One episode of possible aspiration, treated with antibiotics Sep., 2010	37	Chest infection 15th Nov-22nd Nov., 2011 Chest infection 9th Dec-12th Dec., 2011
29	Chest infection April 2011		

Table 29: Serious adverse events

Breath-stacking group		MI-E group	
ID	**Adverse event**	**ID**	**Adverse event**
2	Died at a hospice 10/01/2010 Expected death	4	Hospital admission with aspiration 17/01/2010 Died in hospital 17/01/2010
3	Died at home - 27/10/2010 Expected death	7	Hospital admission with chest infection 19/12/2010 Died in hospital with bi basal pneumonia 25/12/2010
5	Died in the hospital with chest infection 04/04/2010	12	Died at home, mask fell off during sleep 23/10/2011
6	Died at home - 19/11/2012 Expected death	14	Died in the hospital with end stage disease – 29/09/2010
8	Died in the hospital following a stroke – 17/06/2010	15	Hospital admission with chest infection 12/08/2010 Hospital admission with aspiration requiring tracheostomy 15/09/2010 Died in hospital with chest infection 14/12/2010
9	Died at home - 12/12/2011 Expected death	19	Died at home - 03/10/2010 Sudden unexpected death
11	Attended A&E – treated for chest infection - 25/10/2010 Died at home - 18/01/2012 Expected death	20	Died at home - 10/11/2010 Expected death
13	Hospital admission with chest infection May 2011 (2 days)		
18	Died in the hospital following a heart attack (had obesity, complicated diabetes) - 19/04/2011	23	Died at home - 11/03/2011 Expected death
21	Died in the hospital following a severe fall – 20/11/2010	24	Died at home - 29/10/2011 Expected death
22	Died at home - 27/08/2011 Expected death	30	Hospital admission with urine retention 07/07/2011 Died in hospital with chest infection 27/12/2011
26	Died in the hospital – 05/06/2011 Fall and head injury might have contributed to death	33	Hospital admission with chest infection 23/07/2011 Hospital admission with mucous plugging 11/08/2011 Died in hospital with chest infection 17/08/2011
29	Died at home – 24/10/2012 Expected death	37	Died at home - 25/04/12 Expected death
32	Died at home - 31/07/12	38	Died at home - 02/07/12

	Expected death		Expected death
35	Hospital admission with mucous plugging – January 2012		
36	Died at home - 18/09/12 Expected death	41	Died at home - 18/04/12 Expected death
39	Died in hospital with chest infection 26/11/2011		

3.8.12) Survival

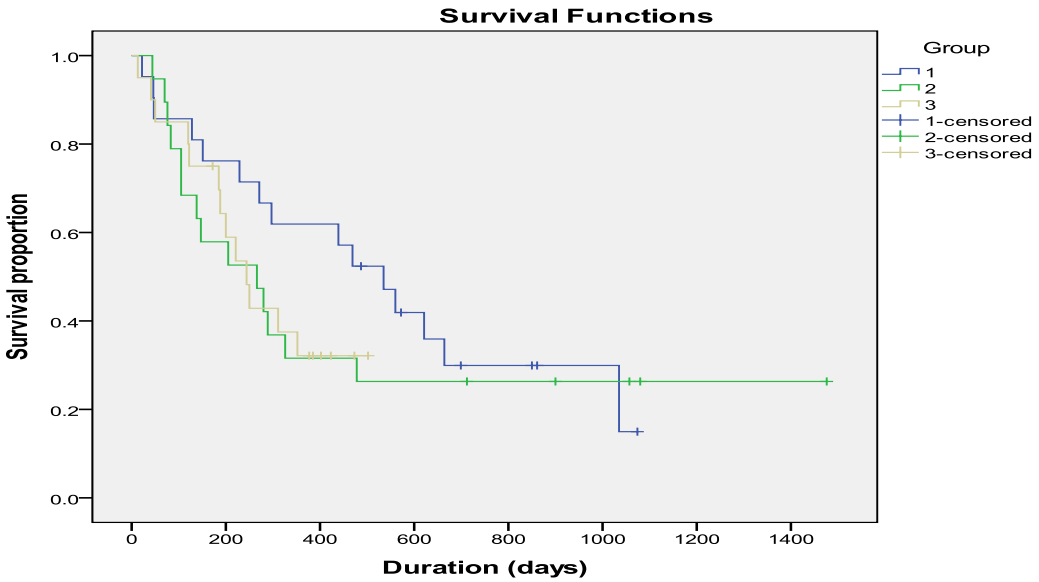
For this study death has been considered as the endpoint to define survival[210]. For survival analysis, a control (NIV only) group comprising of 20 consecutive eligible patients, offered NIV in our centre, once recruitment into the interventional arms, was completed. The survival data of this control group was gathered retrospectively in order to compare the survival figures of interventional groups against no intervention control group. The control group was not randomised but was matched with interventional groups for the prognostic variables used for minimisation. It was felt that, with some limitations, studying the survival of a no intervention control group will allow better appreciation of the survival benefit offered by the cough augmentation techniques.

Table 30 summarises the median survival (days) in the three groups and sub-groups by bulbar function. Figure 19 presents the Kaplan-Mier curves. Median survival in the breath-stacking group was 535 days, 266 days in the MI-E group and 244 days in the NIV only control group. The trial was not powered to detect survival differences with statistical significance; different values in the three groups did not reach statistical significance. Tables 32 and 33 examine survival in relation to the bulbar function.

Table 30: Median (range) survival (days)

Intervention	Breath-stacking group	MI-E group	Standard care	P value*
Overall survival	535 (22-1074)	266 (44-1476)	244 (13-502)	0.54
Good bulbar function	560 (22-861)	289 (70-1476)	280 (41-502)	0.90
Poor bulbar function	229 (47-1074)	138 (44-326)	120 (13-352)	0.08
* Log Rank (Mantel-Cox)				

Intervention	Breath stacking	Standard care	HR* (95% CI)	P value*	P value**
Overall survival	535 (22-1074)	244 (13-502)	0.66 (0.30, 1.43)	0.29	0.16
	MI-E	**Standard care**			
Overall survival	266 (44-1476)	244 (13-502)	0.87 (0.40, 1.91)	0.74	0.79
* Cox regression ** Generalised Wilcoxon test					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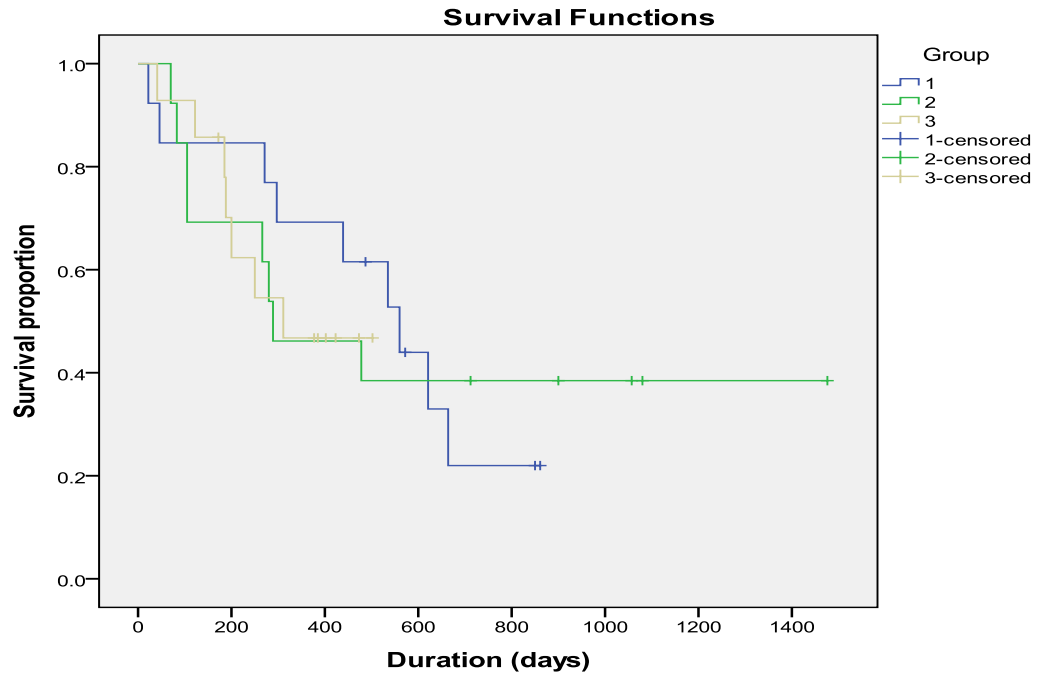
0.8
0.6
0.4
0.2
0.0
0
200
400
600
800
1000
1200
1400
Duration (days)
Group
1
2
3
1-censored
2-censored
3-censored


Survival Functions
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0.8
0.6
0.4
0.2
0.0
0
200
400
600
800
1000
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1400
Duration (days)
Group
1
2
3
1-censored
2-censored
3-censored

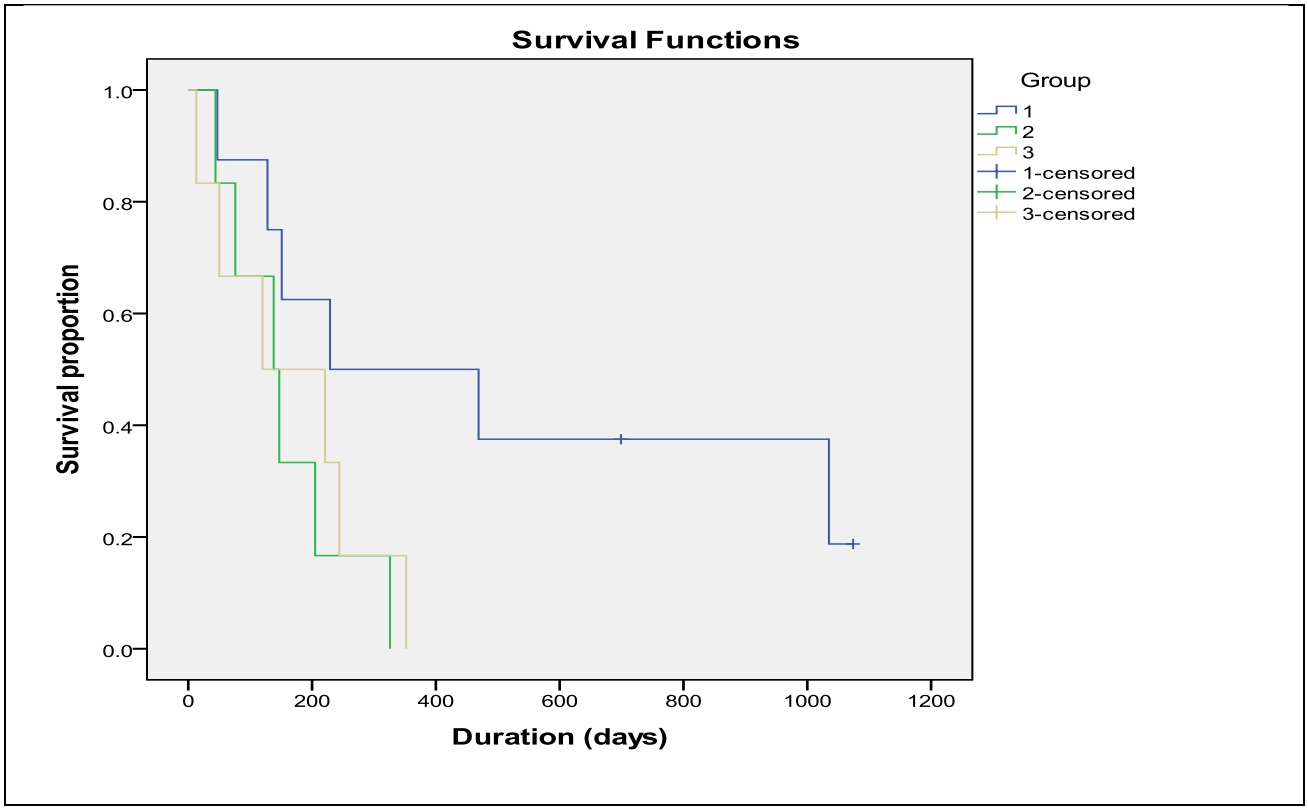


Figure 19: Kaplan Meier survival curves

(Top – patients with good or moderately impaired bulbar function; Bottom: patients with severely impaired bulbar function. Group 1 – breath-stacking; Group 2 – MI-E, Group 3 – NIV only)

Table 31: Means and Medians for Survival Time (whole cohort)

	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
Group	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
1	549.867	84.148	384.938	714.797	535.000	87.312	363.868	706.132
2	525.895	132.416	266.359	785.431	266.000	96.488	76.883	455.117
3	283.175	38.929	206.875	359.475	244.000	35.607	174.210	313.790
Overall	550.120	74.705	403.697	696.542	289.000	41.336	207.982	370.018

a. Estimation is limited to the largest survival time if it is censored.

Table 32: Means and Medians for Survival Time in patients with good - moderately impaired bulbar function

	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
Group	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
1	509.396	77.215	358.055	660.737	560.000	98.124	367.677	752.323
2	696.615	173.364	356.821	1036.410	289.000	127.019	40.043	537.957
3	334.708	45.876	244.792	424.624	280.000	.	.	.
Overall	666.075	99.007	472.021	860.129	478.000	149.516	184.949	771.051

a. Estimation is limited to the largest survival time if it is censored.

Table 33: Means and Medians for Survival Time in patients with severely impaired bulbar function

	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
Group	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
1	523.438	151.013	227.451	819.424	229.000	224.860	.000	669.726
2	156.000	41.089	75.465	236.535	138.000	43.478	52.782	223.218
3	166.667	52.499	63.769	269.564	120.000	104.716	.000	325.243
Overall	306.175	74.541	160.074	452.276	151.000	64.846	23.902	278.098

a. Estimation is limited to the largest survival time if it is censored.

3.8.13) Discussion

Patients with MND having weakness in their breathing muscles struggle to clear airway secretions. This predisposes them to recurrent chest infections and adversely affects their quality of life. Due to the paucity of research in this area, there is no clear consensus about how best to help such patients. This work aims to address this gap in knowledge.

There was no statistically significant difference in the two groups in terms of pulmonary morbidity. However, from a clinical point of view breath-stacking seems to be an effective cough augmentation modality for prophylactic day-to-day domiciliary use. There was a trend (non-significant) for the duration of chest infections and chance of hospitalisation to be less in the MI-E group. This observation is supportive of another prospective uncontrolled study by Vitacca *et al.* which demonstrated that MI-E provided in community in the event of a chest infection reduced hospitalisations. Although the trial was not powered for survival analysis, striking (though non-significant) difference in survival was observed in breath-stacking group highlighting the possibility that simple measures might be as effective as mechanical aids. The quality of life indices also showed a positive trend in the breath-stacking group in several relevant quality of life domains. Importantly the study has demonstrated that survival can be prolonged without detriment to the quality of life with both devices.

From the patients' perspective, most patients with good bulbar function used both devices with enthusiasm. Having access to MI-E was described by some patients as lifesaving and invigorating while breath-stacking was described as light weight, easy to use equipment which helped to stretch the lungs. In the overall study population, survival was closely related to the level of compliance with NIV. In the MI-E group, 6 patients (4 had poor bulbar function) were poorly compliant with NIV and died within 3 months of randomisation. Most of these patients also found the minimally effective pressure of MI-E intolerable. On the contrary only 2 of 8 patients with poor bulbar function in the breath-stacking arm were poorly compliant with NIV, one of whom failed to breath-stack because of poor inspiratory effort and died within 6 weeks of randomisation. Three patients in the breath-stacking group died of unnatural causes (stroke, fall, myocardial infarction), median survival 46 days. No significant adverse effects specifically relating to the use of MI-E or breath-stacking were reported in either group, except that the patients with severe bulbar dysfunction found the pressure delivered by MI-E intolerable. There were 3 patients in the MI-E arm who believed that they would not have

survived in the absence of this intervention. These 3 patients are still alive, over 3 years post-randomisation. Another patient, who used breath-stacking very well till up to one year in the trial, felt that breath stacking was becoming ineffective for him and he had to be provided with MI-E by the community services, which he used up to 6 times per hour for symptomatic relief in the last days of his life.

Given the very heterogeneous and progressive nature of MND, a conclusion that a particular cough augmentation technique is better for all the patients, is difficult to draw from the results of this small scale randomised study. Our study, however, provides some preliminary evidence in support of routine use of breath-stacking technique as first line therapy in patients with MND requiring intervention with NIV for respiratory failure. Patients need to be assessed on an individual basis and MI-E may be offered to the patients with profound respiratory muscle weakness who may not be able to achieve voluntary insufflation and where the breath-stacking technique becomes ineffective with disease progression. Also, MI-E may have a role in a hospital setting and when a chest infection develops. A larger multi-centre study is required to explore these potential benefits and to address the limitations which have been uncovered during the conduct of this initial small-scale interventional trial.

3.8.14) Limitations

This study has limitations due to the small number of patients included and being a single centre trial. Robust data were not available in the literature upon which to base the power calculations for this study. Although a similar number of patients were sufficient to demonstrate the benefits of intervention with NIV in patients with MND, clearly this number was insufficient to demonstrate statistically significant differences when interventions aimed at improving secretion clearance and preventing chest infections, were added to NIV. The data from this trial suggest that a cohort of 150 patients would be required to have sufficient power. Such a large study would be expensive and require multi-site participation. The lack of an NIV only control group for the analysis of pulmonary morbidity is another limitation. A controlled trial may be controversial as evaluating breath-stacking or MI-E against no intervention may be considered unethical.

This study involved frail patients with advanced MND and hence is inherently difficult to conduct. The majority of the study participants were too disabled to attend hospital for their follow-ups and hence a substantial number of follow-up visits were done at the patients' homes. In this regard it was not possible to record patients' weight at some follow-up visits.

It was felt that having multiple tests of respiratory function was technically difficult and tiring for the patients. Maximum inspiratory pressure and maximum expiratory pressure can be used to assess differential strength in the inspiratory and expiratory muscles respectively. However, we could not record these pressures and only FVC and PCF were recorded. It was considered that these two parameters are more clinically relevant and are sufficient to address the aims of the study. Moreover, it has been reported that inspiratory and expiratory muscles are proportionally affected in MND[148].

Some authorities recommend the use of abdominal thrust in the exsufflation phase of both the MI-E and breath stacking techniques[211]. However, this was not included in the study protocol as we considered that frail patients with advanced MND might not tolerate this procedure very well.

The study participants were given the opportunity to record their comments about their respective device in their diaries and also, they were specifically asked about their opinion of

using their respective device. However, no formal qualitative approach or patient satisfaction questionnaire was utilised in the study.

As compliance with NIV is the most important predictor of survival, it is now clear from the results we have obtained that it would have been beneficial to include a stricter criterion for compliance with NIV in the inclusion criteria. Patients in this study were offered participation in the study 15 days after initiating NIV, but this stage appears to have been too early to make a firm conclusion about their compliance with NIV. The lack of this information in the randomisation process has resulted by chance in a higher number of non-compliant patients being assigned to the MI-E technique.

Blinding in randomised clinical trials improves validity. Use of clinical judgement was required when deciding upon the number of episodes of chest infection and the duration of chest infections. This carried the risk of introducing the researcher's bias. Lack of blinding of the evaluating physician is another limitation in this trial. This limitation could have important implications, had the results been significantly in favour of one of the two interventions.

This study does not have a true control group as evaluating MI-E/BS against no intervention could be considered unethical. However, we felt that the magnitude of survival benefit could not be appreciated without a control group. Hence, once recruitment into the interventional arms was completed, a non-randomised but prognostically matched control group, selected by the same inclusion/exclusion criteria was added for survival analysis. Such post hoc control group has its own limitations.

3.8.15) Conclusions

This study has provided important pilot information for a future larger scale trial of cough assist devices in MND. Important observations include:

1. Prevention of chest infections and maintenance of lung compliance is an important aspect in the overall care of patients with MND.
2. The strength of cough may be impaired in patients with MND and the provision of a suitable cough augmentation technique may prevent chest infections, hospital admissions and improve quality of life.
3. Patients with severe bulbar dysfunction may find breath stacking difficult to use due to difficulty in closing the glottis which is required to hold successive breaths.
4. Patients may find the minimally effective pressure of the MI-E machine difficult to tolerate.
5. Chest infections may not be prevented with cough augmentation if hypersialorrhea and aspiration of saliva cannot be prevented.
6. Breath stacking may be an effective intervention for the prevention of chest infection in the early stages of MND.
7. The ability of the MI-E machine to simulate normal human cough and its ability to generate cough pressures comparable to normal human cough makes it particularly useful in the advanced stages of the disease or in the setting of an established chest infection.
8. MI-E may be useful in the hospital setting, reducing the required duration of antibiotic treatment and length of stay, in the event of a chest infection.
9. Compliance with NIV is an important predictor of survival and is crucial in the evaluation of any potential additional benefit from cough augmentation techniques.

CHAPTER 4

TRANSCUTANEOUS CARBON DIOXIDE MONIOTRING

4.1) Introduction

As with most other skeletal muscles of the body, the respiratory muscles are also affected in MND. Respiratory muscle function is an important predictor of quality of life (QoL) and hypoventilatory respiratory failure is the commonest cause of death in MND[81]. Early diagnosis of respiratory failure and treatment with non-invasive ventilation (NIV) offers the best survival advantage currently available, as well as an improved quality of life[125]. The UK National Institute for Health and Clinical Excellence and American Academy of Neurology recommend regular screening for respiratory failure, following a diagnosis of MND[58]. Symptom evaluation and respiratory function tests (most commonly forced vital capacity, maximal inspiratory mouth pressure and sniff nasal inspiratory pressure) are used to screen the patients for respiratory failure (PCO_2 > 6 kPa by definition). Currently there is no single test of respiratory muscle strength which can predict hypercapnia with high sensitivity and specificity. Moreover, volitional tests of respiratory function depend on patients' motivation for performing the manoeuvre and have serious limitations in patients with severe bulbar weakness[100]. The gold standard for measuring PCO_2 in the blood is arterial blood gas analysis. However this is an invasive test which requires specialist medical skills and can cause considerable discomfort to the patients, especially if repeated samples are needed. It can potentially lead to complications such as arterial thrombosis, pseudoaneurysm formation and infection at the puncture site.

A non-invasive test to monitor PCO_2 on a regular basis in MND patients would be very useful. Such a test would also be of benefit following the initiation of NIV, for periodic monitoring of PCO_2, to confirm the effectiveness of NIV at the prescribed pressure settings. TOSCA *500* (Linde Medical Sensors) is a lightweight portable device which can measure PCO_2 and oxygen saturation (SpO_2) with a single sensor attached to the ear lobe (Figures 20/21). TOSCA incorporates the physiological principle that CO_2 gas is able to diffuse through the skin and can be detected by a sensor at the skin surface. Another advantage of TOSCA is that it can provide a continuous reading, allowing overnight monitoring of PCO_2 and SpO_2 to detect nocturnal hypercapnia and oxygen desaturations. Several studies have looked at the accuracy of this device in various clinical settings such as sleep laboratories, emergency department, intensive care unit and in routine respiratory practice[212-214]. To our knowledge, there are currently no studies on the potential benefit of TOSCA *500* in assessing respiratory

failure in patients attending MND clinics. We hypothesized that TOSCA can accurately measure PCO_2 and if recorded at regular intervals during follow up clinical assessments, may help in the early diagnosis of respiratory failure.

4.2) Study design

This is a prospective observational cohort study consisting of 40 consecutive MND patients attending the Sheffield Motor Neuron Disorders clinic.

4.3) Primary research question

Is recording transcutaneous carbon dioxide level with a TOSCA monitor accurate in patients with MND?

4.4) Standard protocol approval, registration and patient consent

The study protocol was approved by Bradford research ethics committee, reference 10/H1302/96. Written informed consent was obtained from all patients (or carers of patients) participating in the study.

4.5) Study setting and population

The study was carried out at the specialist neuromuscular outpatient clinic at the Royal Hallamshire Hospital, Sheffield. In this clinic patients with MND are routinely screened for respiratory impairment. A cohort of 40 consecutive diagnosed patients with MND, who gave informed consent, was recruited irrespective of the duration of their disease or respiratory status. The only exclusion criterion was inability (due to mental capacity) or unwillingness to give informed consent. The characteristics of study participants are summarised in Table 34.

Table 34: Characteristics of the study participants

Characteristics	n
Gender (M:F)	26:14
Mean (range) age (years)	61 (26 - 85)
Mean (range) duration of disease (months)	43 (3-157)
Mean (range) $PaCO_2$ (kPa)	5.08 (4.1 – 6.2)
Mean (range) $PtCO_2$ (kPa)	5.17 (4.4 - 6.2)
Mean (range) difference $PaCO_2$ – $PtCO_2$	-0.08 (-0.93 - 0.95)

4.6) Study tools

Arterialized capillary blood gas analysis is an acceptable alternative to arterial blood sampling[186]. This method has been reported to be less painful and can be safely done by para-medical staff. There is a strong correlation and limits of agreement between arterial and arterialized blood samples with respect to pH and PCO_2[187]. Arterialized capillary blood gas analysis was used in this study to measure the arterial pressure of carbon dioxide ($PaCO_2$), as the less invasive and painful method of the two techniques available. A heat rub cream was applied to the ear lobe for 10-15 minutes to allow vasodilatation and arterialization of the ear lobe capillary bed. The ear lobe was then pierced with a spring loaded needle and blood collected in a capillary tube. The blood sample was analysed by a Radiometer ABL 700 blood gas analyser without delay. Transcutaneous carbon dioxide level ($PtcCO_2$) was recorded from the opposite ear lobe, using TOSCA *500*, operated in accordance with the manufacturer's operating manual. A disposable ear clip was used to attach the sensor from the TOSCA monitor to the ear lobe. A contact gel was applied between the sensor and the skin to facilitate diffusion. The device was operated on a "QUICKSTART" mode which warms the sensor to a temperature of 42°C (to achieve a local hyperaemia, increasing the arterial blood supply in the dermal capillary bed below the sensor) and gives the reading in 10-15 minutes.

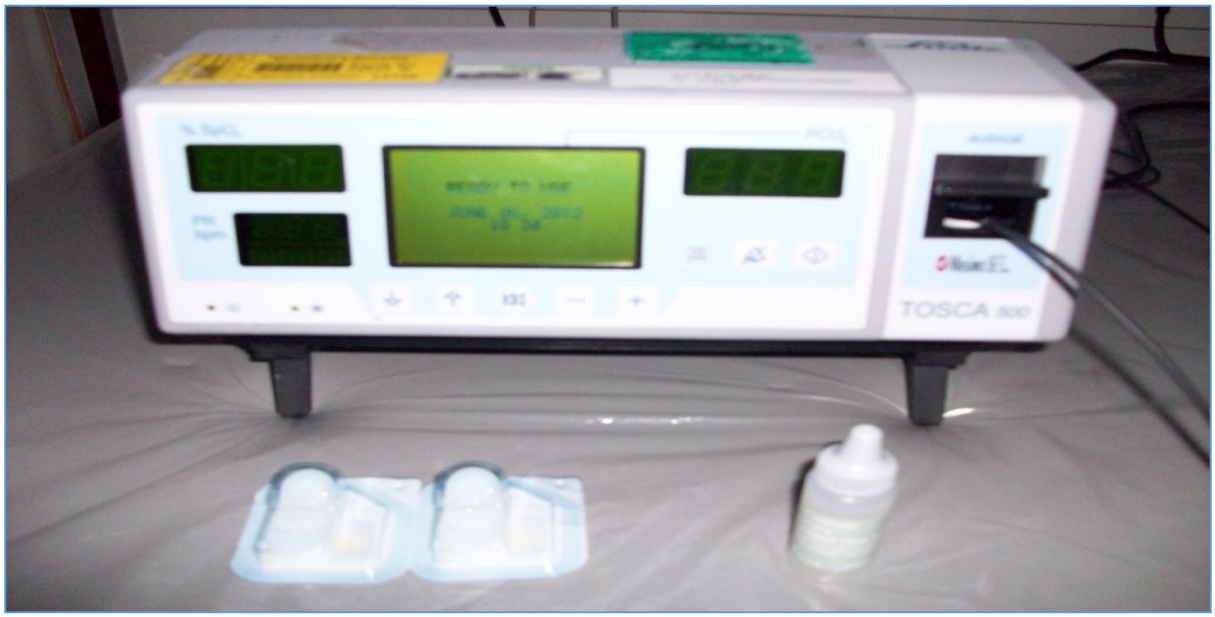


Figure 20: TOSCA *500* along with ear clips and contact gel

Figure 21: A clip attached to the ear lobe

4.7) Measurements

An arterialized ear lobe capillary blood sample (ELCS) was taken while a researcher noted the transcutaneous CO_2 reading simultaneously in a standardised data collection form.

4.8) Statistical analysis

The power calculation is based on standard deviations (0.13 – 0.67 kPa) reported in previous studies of patients with respiratory disease, of the difference between $PtcCO_2$ and $PaCO_2$. As this is an agreement study, the focus is on estimating the standard deviation of the difference between $PaCO_2$ and $PtcCO_2$ to an acceptable precision. From statistical tables, a sample size of 40 ensures that the difference is not overestimated by more than 20% with 95% probability. For example, if the true difference is 0.5 kPa, the probability that the estimated difference is 0.6 kPa or greater is 5%.

The Bland-Altman method is used for the analysis of agreement between the two methods [215]. The absolute difference between the two measurements ($PaCO_2$ – $PtCO_2$) is plotted against the average of the two measurements and the limits of agreement established. The 95% limits of agreement, defined as the difference of error within which 95% of the patients are expected to lie, are established. The Pearson correlation coefficient is used to demonstrate the presence or absence of a relationship between the two measurements. Descriptive data are presented as means with ranges. Statistical analysis was conducted using PASW version 18 (SPSS Inc. PASW Statistics 18, Release Version 18. 2009, Chicago, IL.).

4.9) Results

Paired arterialised capillary blood and transcutaneous carbon dioxide measurements were taken from 40 consecutive patients with MND (Table 35). Figure 22 illustrates the data as a scatter plot with a line of agreement. The mean difference (bias) between the two measurements was -0.08 kPa, with a standard deviation (SD) of 0.318 and standard error of the mean (SEM) of 0.05. Pearson's correlation coefficient of 0.808 showed a statistically significant relationship between the two methods ($p<0.001$), but not that they necessarily agree. The Bland-Altman plot (Figure - 23) showed overall good agreement between the two measurements with 95% limits of agreement (bias ± 1.96SD) between 0.553 and -0.719 kPa. In 22 patients the $PtcCO_2$ reading was higher than the $PaCO_2$ reading but no consistent numerical relationship was identified between the two measurements and hence the application of a correction factor cannot be recommended.

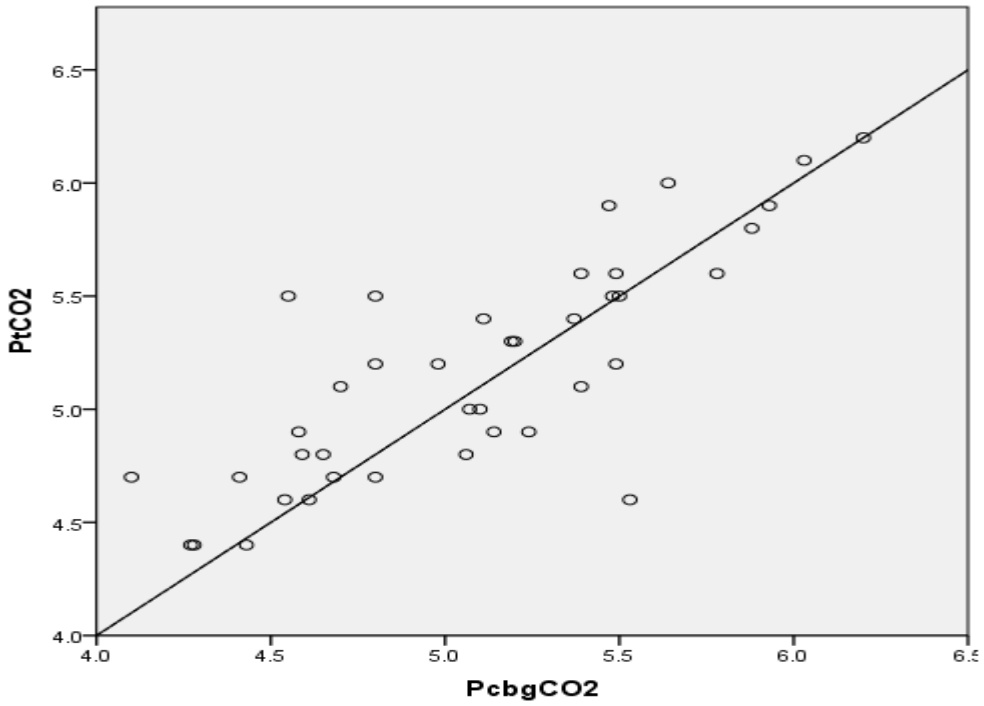


Figure 22: Scatter plot with line of agreement showing the PCO_2 measurements taken by two methods. Pearson's correlation coefficient of 0.808

Table 35: $PaCO_2$ and $PtCO_2$ values of the study participants. The values shown in bold have a difference > 0.5 kPa. The values shown in red indicate where the patient had a PCO2 level above the upper limit of normal (>6.0 kPa)

No.	$PaCo_2$	$PtcCO_2$	Difference	No.	$PaCo_2$	$PtcCO_2$	Difference
1	5.47	5.9	-0.43	**21**	**4.1**	**4.7**	**-0.6**
2	**4.55**	**5.5**	**-0.95**	22	5.78	5.6	0.18
3	**5.53**	**4.6**	**0.93**	23	5.24	4.9	0.34
4	**4.8**	**5.5**	**-0.7**	24	4.98	5.2	-0.22
5	4.58	4.9	-0.32	25	5.19	5.3	-0.11
6	5.14	4.9	0.24	26	5.11	5.4	-0.29
7	5.48	5.5	-0.02	27	4.41	4.7	-0.29
8	5.06	4.8	0.26	28	5.1	5.0	0.1
9	4.61	4.6	0.01	28	5.49	5.2	0.29
10	4.43	4.4	0.03	30	5.49	5.6	-0.11
11	4.65	4.8	-0.15	31	5.64	6.0	-0.36
12	6.03	6.1	-0.07	32	5.07	5.0	0.07
13	5.2	5.3	-0.1	33	4.27	4.4	-0.13
14	4.8	4.7	0.1	34	5.93	5.9	0.03
15	4.68	4.7	-0.02	35	5.39	5.1	0.29
16	4.54	4.6	-0.06	36	5.37	5.4	-0.03
17	4.28	4.4	-0.12	37	4.59	4.8	-0.21
18	4.8	5.2	-0.4	38	5.39	5.6	-0.21
19	4.7	5.1	-0.4	39	5.88	5.8	0.08
20	6.2	6.2	0	40	5.5	5.5	0

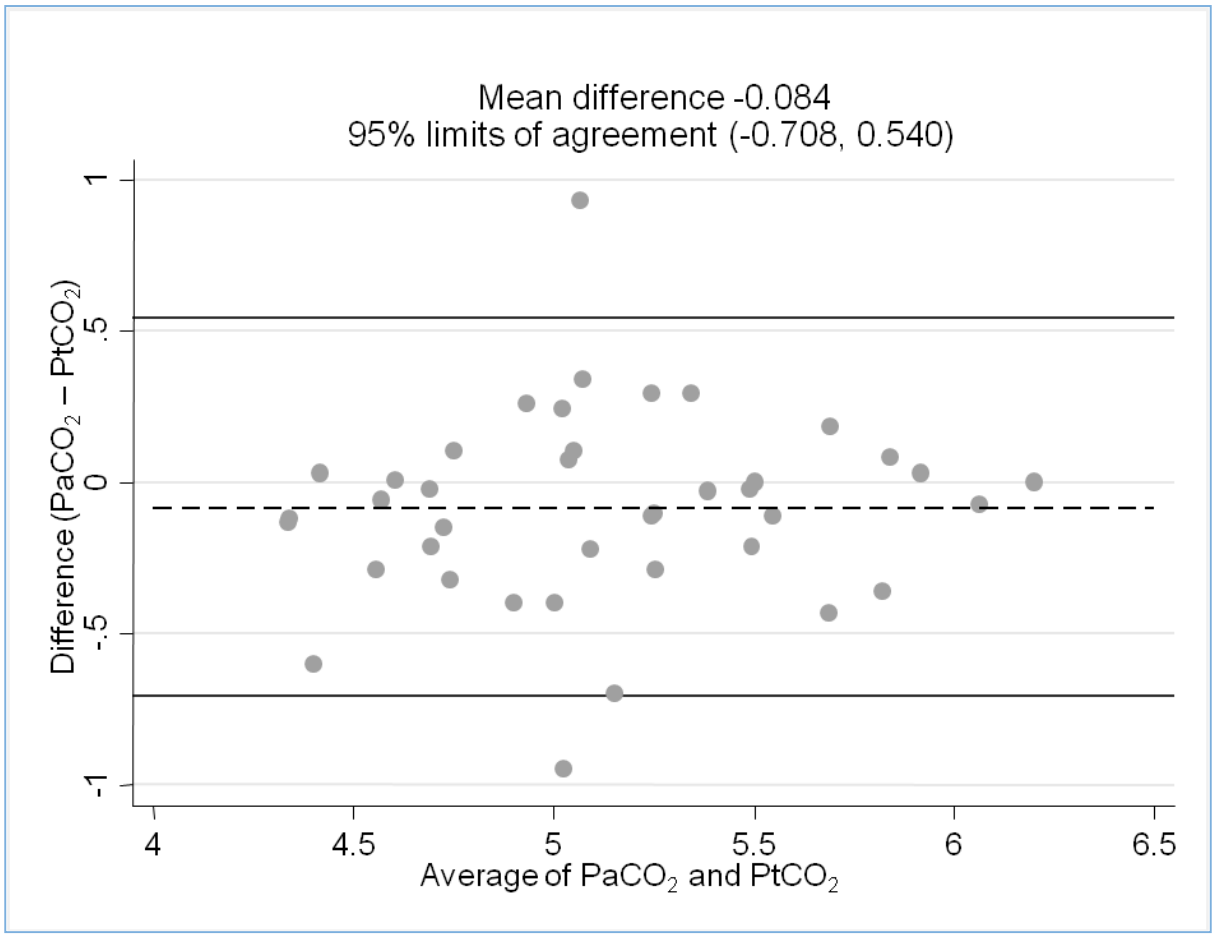


Figure 23: Bland-Altman plot of the difference between the two measurements against the average of the two measurements

4.10) Discussion

Our day to day clinical experience in patients with MND suggests that the TOSCA monitor is reasonably accurate for measuring PCO_2. However, because of the limited published literature, $PtcCO_2$ is not commonly utilised in the assessment of respiratory function in MND patients. This study demonstrates that, with appropriate caution, the TOSCA can be a useful clinical device for non-invasive monitoring of PCO_2. In our cohort of patients, recording PCO_2 transcutaneously would not have led to a false positive or false negative diagnosis of respiratory failure i.e., when $PaCO_2$ was above 6.0 kPa, $PtcCO_2$ was also above 6.0 kPa and vice versa.

Although it is subjective to define a "clinically acceptable" difference between the two methods, we consider a difference of < 0.5 kPa to be a clinically acceptable compromise for the use of a non-invasive test. The normal range of PCO_2 is 4.5-6.0 kPa, and a difference of 0.4 kPa is unlikely to affect clinical management. Moreover, $PtCO_2$ is more likely to be higher than $PaCO_2$, and hence a diagnosis of respiratory failure is unlikely to be missed. A difference of > 0.5 kPa, between the two measurements, was observed in four subjects, with no obvious explanation. All study participants were clinically stable and hence abnormal tissue perfusion, which can affect either method, causing an erroneous reading is unlikely. Obtaining an accurate ELCS is dependent on technique and errors in the blood sampling technique may be responsible for the discrepant readings in this study. Adequate arterialisation should be achieved by allowing sufficient time for vasodilatation, following the application of the heat rub cream. Squeezing the ear lobe to draw the blood sample should be avoided as it may cause venous and lymphatic contamination of the sample, thus affecting the accuracy of the results. Exposure of the blood to the atmospheric air should be minimised and the blood sample drawn directly into the capillary tube from the skin surface.

Interestingly, our results are similar to the small number of previous reports assessing the accuracy of the TOSCA monitor. In a study involving transcutaneous PCO_2 monitoring during initiation of NIV in patients with acute hypercapnic respiratory failure, the mean difference between $PaCO_2$ and $PtCO_2$ was 0.61 kPa and Bland-Altman limits of agreement ranged from -0.5 – 1.76 kPa[6]. In another study of patients attending the emergency department, the mean difference between $PaCO_2$ and $PtCO_2$ was 0.02 kPa and the Bland-Altman limits of

agreement were ± 0.9 kPa[212]. A study evaluating TOSCA in routine respiratory practice reported a PCO_2 difference of above 1 kPa in four of 48 measurements[214]. Most authors concluded that although TOSCA is a clinically useful device, significant individual variance between $PaCO_2$ and $PtCO_2$ cannot be excluded with certainty and hence transcutaneous PCO_2 monitoring cannot completely replace blood gas analysis.

A deficiency in transcutaneous monitoring, as opposed to blood sampling is that it does not provide detailed assessment of acid-base status. However this is less of an issue in patients with MND as the onset of respiratory failure is gradual in most cases. It is likely that compensation will have taken place and that the pH is within the normal range so that lack of this information makes little difference in the management of this patient group. A limitation of this study is the narrow range of PCO_2 studied (4.1 – 6.2 kPa). One may argue that higher values would produce a greater difference. In a similar study of eighty patients with acute respiratory failure (four patients with ALS) the range of PCO_2 studied was 5.6 – 11.8 kPa. The authors concluded that the agreement between the two measurements is independent of the level of $PaCO_2$[216].

From the patients' perspective, although little discomfort was reported from the capillary ear lobe sample, a preference for the non-invasive method was expressed. There were no complications related to the use of the TOSCA *500* device. Whilst both methods can be performed by trained allied health care professionals, the TOSCA method requires much less skill and training to achieve competency, does not require a gas analyser and can be undertaken in the clinic as well as in the community.

Non-invasive monitoring with TOSCA *500* therefore, is a useful device to be utilised for the assessment of MND patients, enabling regular and non-invasive screening for respiratory failure, particularly in patients for whom volitional tests are unreliable or burdensome. As with any test, it is necessary to consider the $PtcCO_2$ readings in the wider clinical context, especially if the readings are not compatible with the symptoms or other tests of respiratory function (e.g., forced vital capacity). We recommend that a $PtcCO_2$ reading of > 6.0 kPa in ALS patients is verified by an arterial blood gas analysis, so that the decision for intervention with ventilatory support is planned without any ambiguity.

CHAPTER 5

VALUE OF PERIODIC TRANSCUTANEOUS CARBON DIOXIDE MEASUREMENTS IN MOTOR NEURONE DISEASE

Screening patients regularly for evidence of respiratory failure is an important facet in the management of motor neurone disease (MND). Currently there is no single test which can predict respiratory failure with high sensitivity and specificity. Moreover, no test of respiratory muscle strength has significant positive predictive power to predict hypercapnia in the subgroup of patients with significant bulbar weakness[100]. Standard current practice is to screen patients for symptoms of respiratory failure and supplement this with one or more respiratory function tests. FVC is the most commonly used respiratory function test in many MND clinics for this purpose.

MND patients with respiratory failure can benefit from non-invasive ventilation (NIV) which has been shown to improve survival as well as quality of life[125]. Although the precise timing for NIV initiation for maximum benefit has not been established in a clinical trial, once an MND patient reaches the stage of respiratory failure the mean survival is only few months. Therefore early detection of respiratory failure may be important. Since the first ever manifestation of impaired ventilation is nocturnal hypercapnia (rising carbon dioxide in the blood during sleep), a simple and non-invasive test to monitor partial pressure of carbon dioxide (PCO_2) in the blood on a regular basis would be very useful in clinical practice. As discussed in the previous chapter, the transcutaneous carbon dioxide (TOSCA) monitor allows transcutaneous measurement of the partial pressure of carbon dioxide ($PtcCO_2$) along with oxygen saturation (SpO_2), with a probe attached to the ear lobe[217].

5.1) Research question

Is recording daytime $PtcCO_2$ regularly with a TOSCA monitor sensitive in the early detection of type II respiratory failure in patients with MND?

5.2) Research Hypothesis

Periodic measurement of $PtcCO_2$ in the clinic, using this non-invasive method will be sensitive for early detection of type II respiratory failure in patients with MND. We hypothesize that during the follow-up assessments we will identify some patients with a raised $PtcCO_2$ (and hence respiratory failure) but otherwise no evidence of respiratory failure i.e., having no symptoms and a preserved FVC. This will allow us to conclude that periodic recording of

$PtcCO_2$ in otherwise asymptomatic patients is a sensitive and specific measure for early detection of respiratory failure in both limb or bulbar onset sub-groups of MND. The patients thus identified may require further evaluation with overnight sleep studies to establish the need for respiratory support.

5.3) Aims of the Study

This study aims to determine whether PtcCO2 is a sensitive and specific test for screening for early type II respiratory failure compared to symptom history or volitional respiratory function tests.

5.4) Study design

This is a prospective observational cohort study consisting of 50 consecutive MND patients.

5.5) Study participants

a) Inclusion Criteria:

1. Age 18 or older
2. Familial or sporadic MND (all forms)
3. Informed consent from patient or designated representative

Exclusion Criteria:

1. Inability or unwillingness to give informed consent.
2. Known respiratory failure or raised PCO2.

5.6) Study setting and plan of investigation

Participants were recruited from the Sheffield Care and Research Centre for Motor Neurone Disorders. On the registration visit, after obtaining an informed consent patients underwent the following assessments:

1. Detailed questioning about the symptoms of respiratory failure (using a standard questionnaire – appendix 1)
2. TOSCA $PtcCO_2$
3. Forced vital capacity (FVC)
4. Sniff nasal inspiratory pressure (SNIP)

Only those patients with a normal $PtcCO_2$ (4.6 - 6 kPa) were recruited. At each 3 monthly subsequent visits patients underwent the following assessments:

1. Detailed questioning about the symptoms of respiratory failure (using a standard questionnaire – appendix 1)
2. TOSCA $PtcCO_2$
3. Forced vital capacity (FVC)
4. Sniff nasal inspiratory pressure (SNIP)

Once respiratory failure was clinically suspected by the treating physician, further follow-up was stopped. The presence of respiratory failure was confirmed with an overnight capnometry.

5.7) Primary outcome measure

The primary outcome measure is the number of patients needed to test to detect one case of respiratory failure which would have not been clinically detected.

5.8) Ethics and governance

This study was reviewed and approved by Bradford Research Ethics committee (Ref. no. 10/H1302/96). It is registered with the research and development department of Sheffield Teaching Hospitals NHS Trust (Ref. STH15921) and has been undertaken in accordance with the research governance regulations.

5.9) Results

A total of 50 patients were recruited. At the time of writing, 27 patients reached the point where respiratory failure was suspected by the treating physician. 13 patients are still under follow-up. 4 patients died unexpectedly and 6 patients were lost to follow-up and hence excluded from the final analysis.

5.9.1) Baseline indices of the study participants

Table 36 summarises the baseline indices of the study participants.

Table 36: Baseline characteristics of the study participants

Parameter	N (range) [SD]
Total number	50
Mean (range) age (years)	60 (27-77) [12.3]
Gender (M:F)	29:21
Mean duration of disease (months)*	39 (6-157) [35.7]
Site of onset: • Limb onset • Bulbar onset • Respiratory onset	 41 (82%) 9 (18%) 0
Mean Bulbar Score • No. with normal to moderate bulbar impairment (score 7-12) • No. with severe bulbar impairment (score 0-6)	10 44 (88%) 6 (12%)
Mean (range) SVC (% predicted)	79% (26-139) [23.3]
Mean (range) SNIP (% predicted)	60% (8-119) [23.4]
Mean (range) $PtCO_2$ (kPa)	5.0 (4.2-5.9) [0.39]

SVC Slow vital capacity

SNIP Sniff nasal inspiratory pressure

$PtcCO_2$ (kPa) Transcutaneous carbon dioxide (kiloPascal)

5.9.2) Evidence of respiratory failure

Symptom history, FVC, SNIP and $PtcCO_2$ were the clinical tools used to screen the patients for respiratory failure at each follow-up visit. Further follow-up was stopped when the patients were clinically suspected to be in respiratory failure as defined in chapter 2. Clinical suspicion of respiratory failure was confirmed with an overnight transcutaneous capnometry. Analysis was carried out to determine the predictive power of these clinical tools to detect respiratory failure (hypercapnia). Table 37 summarises the respiratory parameters at the time when respiratory failure was suspected. These data suggest that the presence of symptoms of respiratory failure is the most powerful tool to predict respiratory failure. FVC and day time $PtcCO_2$ were insensitive as FVC of > 70% of predicted and day time $PtcCO_2$ of < 5.0 kPa was observed in patients where respiratory failure was suspected clinically due to presence of symptoms and those who fulfilled the criteria of respiratory failure on nocturnal capnometry.

Table 37: Respiratory parameters when respiratory failure suspected and confirmed by overnight capnometry

Parameter	N (range)
Number of patients developing respiratory failure	27 (54%)
Duration from disease onset to the development of respiratory failure (days)	974 (431-3702)
Number of patients with symptoms when respiratory failure suspected	27 (100%)
Number of patients with FVC < 50% when respiratory failure suspected	14 (51%)
Number of patients with FVC 50-70% when respiratory failure suspected	7 (14%)
Number of patients with FVC > 70% when respiratory failure suspected	3 (11%)
Number of patients with $PtCO_2$ > 6.0 kPa when respiratory failure suspected	4 (15%)
Number of patients with $PtCO_2$ > 6.0 kPa without any other marker of respiratory failure	0

5.9.3) Symptoms of respiratory failure

In order to have a consistent approach in screening for symptoms of respiratory failure, a questionnaire consisting of 18 possible symptoms of respiratory insufficiency was developed. A detailed search of the literature did not identify any pre-existing questionnaire which could be used for this purpose. The questionnaire was based on symptoms reported by patients with respiratory muscle weakness (in the literature and clinical experience of the investigators)[75,98,218-221]. It was interviewer administered and took 5-10 minutes to complete. The symptoms were divided into three domains i.e., breathing related symptoms, sleep related symptoms and mental/emotional state. This format was partially influenced by the format of the ALS functional rating scale and sleep apnoea quality of life index[191,204]. Each question was answered as yes or no, with one mark awarded for each affirmative answer. The questionnaire was piloted to ensure the questions were easy to understand, clear and open ended. The questionnaire in appendix 1 is the final questionnaire developed following some minor amendments in response to pilot experience.

The most common symptoms (present in at least 1/3rd of the patients at the time of suspected respiratory failure) are reported in table 38. These questions may assist in identifying those at risk and in the decision to investigate a patient further. Cronbach's alpha (α) was calculated as a measure of internal consistency of the responses when respiratory failure was clinically suspected. The Cronbach's α for the analysed cohort of 27 patients was 0.7. A Cronbach's α value between 0.7 and 0.8 is considered as having a strong and positive correlation of the items of a scale.

Table 38: Most common symptoms at the time of suspected respiratory failure

Symptom	**No. of patients (n=27)**
Shortness of breath on exertion (e.g., walking, eating, bathing, dressing etc)	20 (74%)
Noticed any change in breathing	18 (66%)
Difficulty in coughing	12 (44%)
Sleepy during the day (more than usual)	11 (40%)
Interrupted sleep	9 (33%)
Fatigue or lack of energy	10 (37%)
Loss of appetite	9 (33%)

5.9.4) Relationship between symptoms and respiratory function tests

Table 39 and 40 illustrate the relationship between SVC and SNIP and symptoms of respiratory failure respectively. No relationship between respiratory function parameters and number of symptoms of respiratory failure is demonstrated at any of the follow-up time points. Power beyond 12 months, however, is weak due to early deaths and the fact that some patients had not reached that stage of follow-up at the time of writing.

Table 39: Relationship between SVC and symptoms

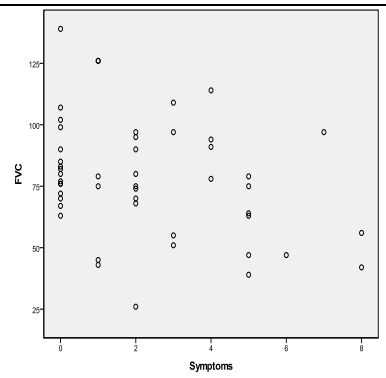
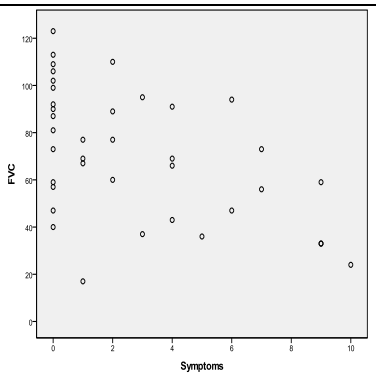
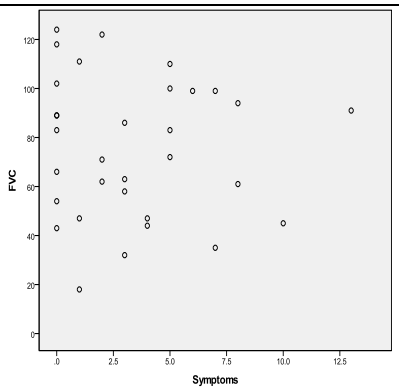
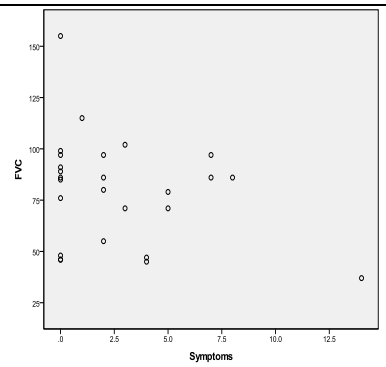
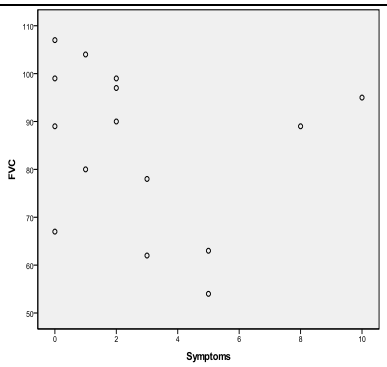
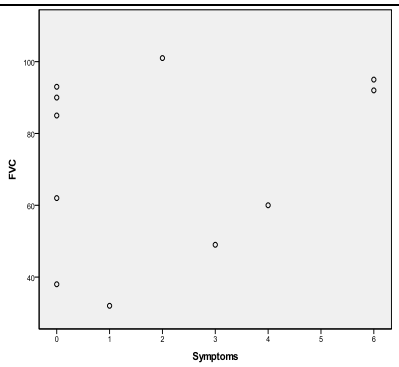
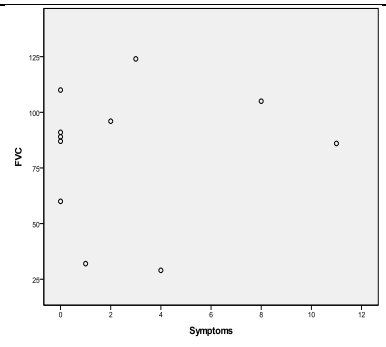
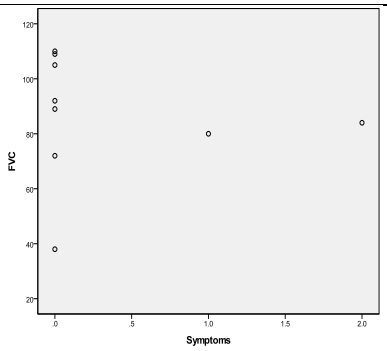
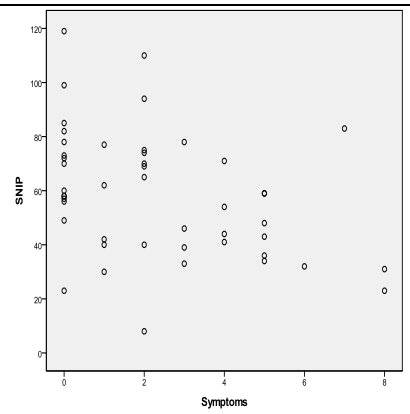
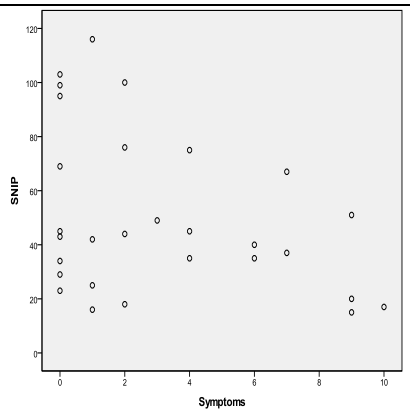
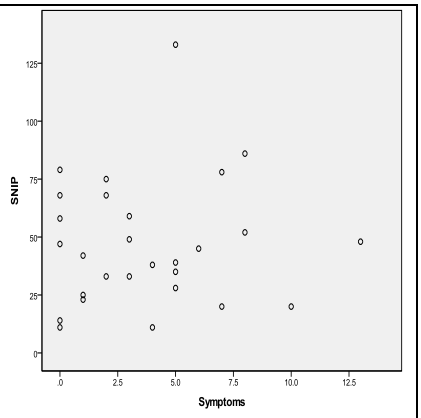
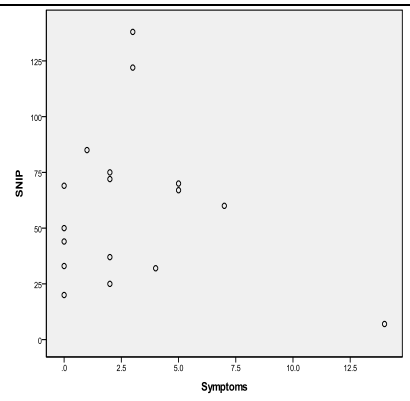
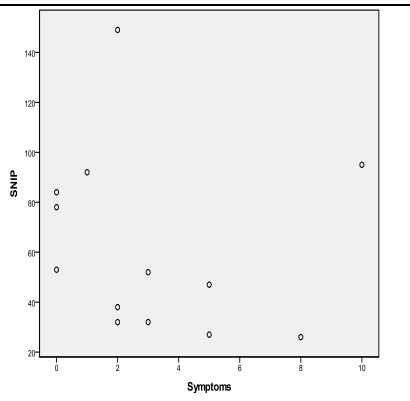
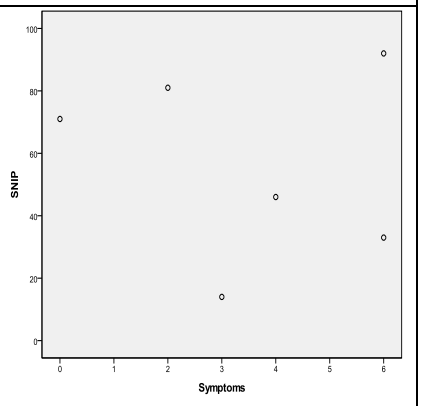
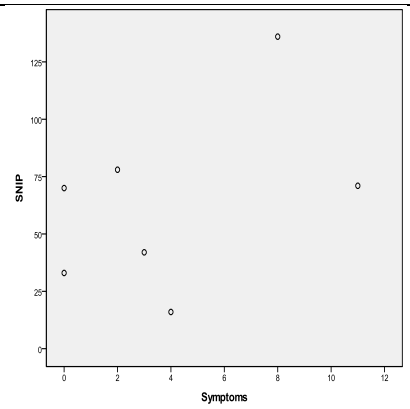
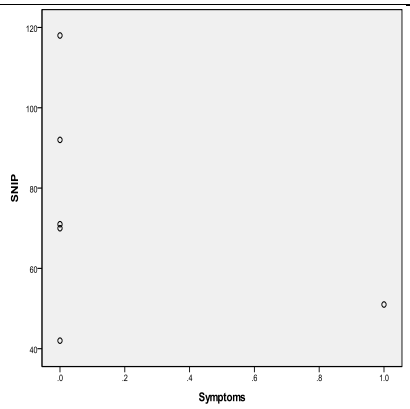
		
Baseline (Pearson Cor. -0.31)	3 months (Pearson Cor. -0.496)	6 months (Pearson cor. -0.055)
		
9 months (Pearson Cor. -0.278)	12 months (Pearson Cor. -0.200)	15 months (Pearson Cor. 0.248)
		
18 months (Pearson Cor. 0.090)	21 months (Pearson Cor. -0.92)	

Table 40: Relationship between SNIP and symptoms

		
Baseline (Pearson Cor. -0.379)	3 months (Pearson Cor. -0.355)	6 months (Pearson cor. -0.072)
		
9 months (Pearson Cor. -0.177)	12 months (Pearson Cor. -0.170)	15 months (Pearson Cor. -0.117)
		
18 months (Pearson Cor. 0.445)	21 months (Pearson Cor. -0.407)	

5.9.5) Relationship between transcutaneous carbon dioxide level and respiratory function tests

Table 41 and 42 illustrate the relationship between SVC and SNIP with $PtcCO_2$ respectively. No relationship between respiratory function parameters and $PtcCO_2$ is demonstrated at any of the follow-up time points. Power beyond 12 months, however, is weak due to early deaths and the fact that some patients had not reached that stage of follow-up at the time of writing.

Table 41: Relationship between SVC and $PtcCO_2$

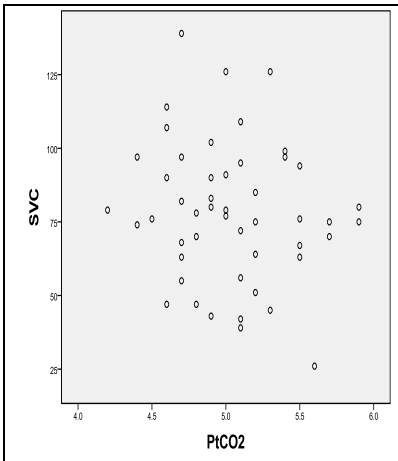
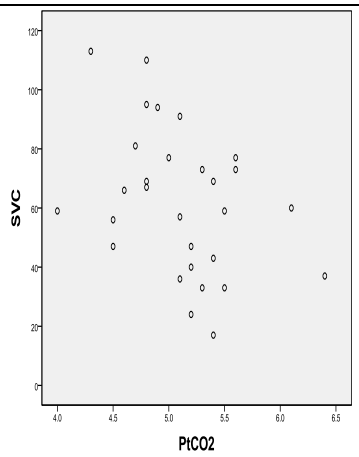
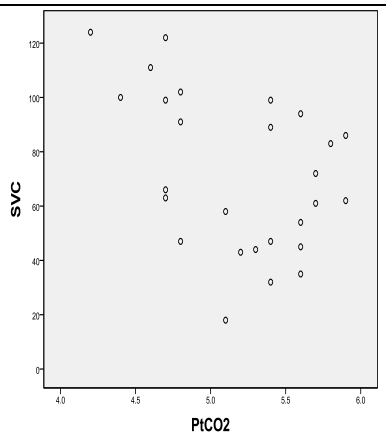
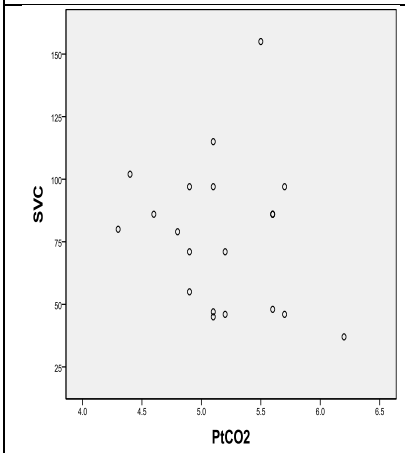
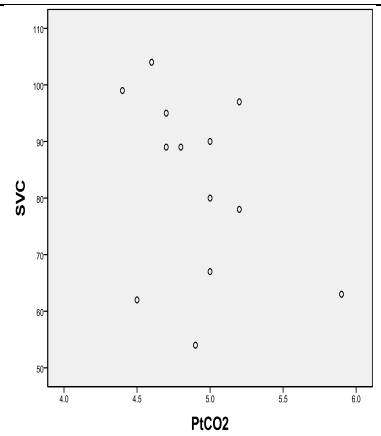
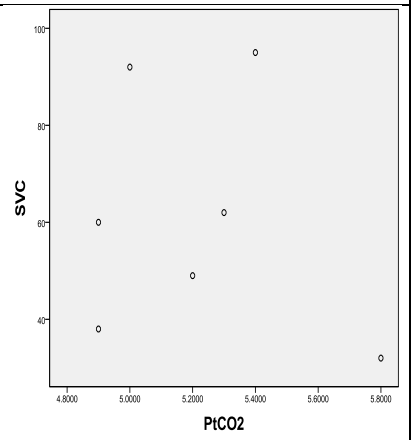
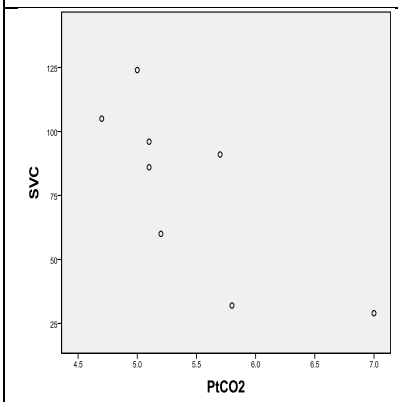
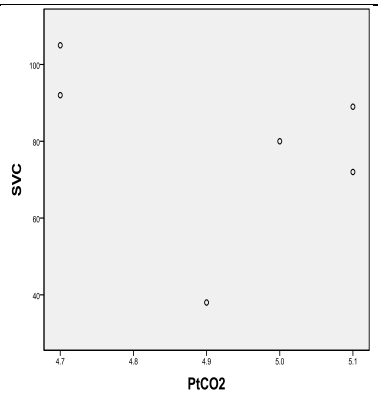
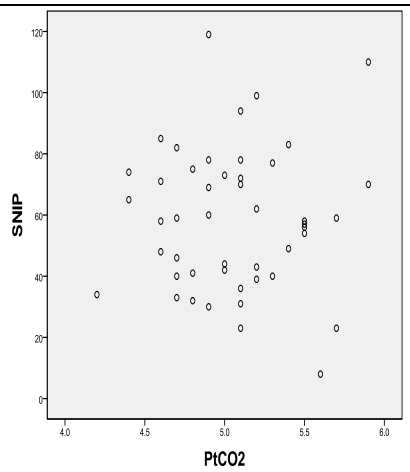
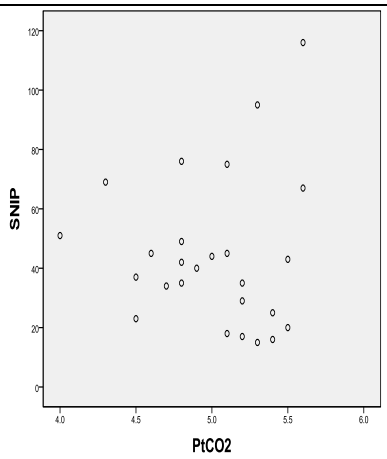
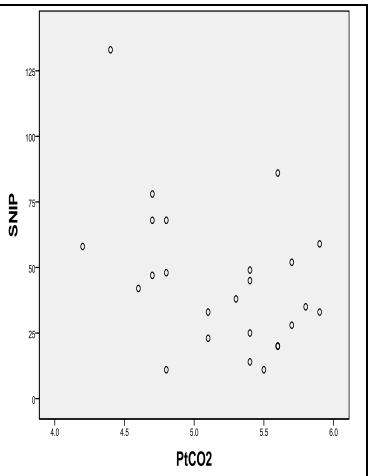
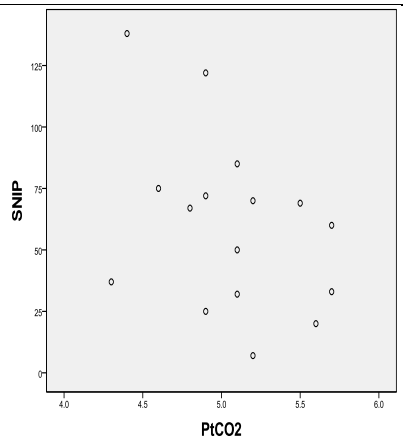
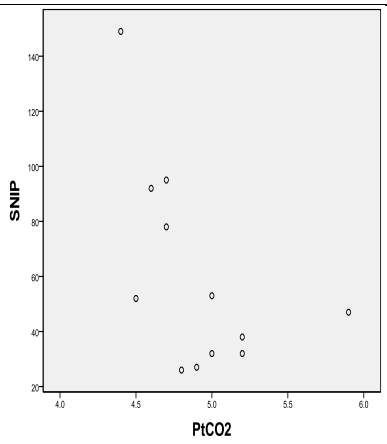
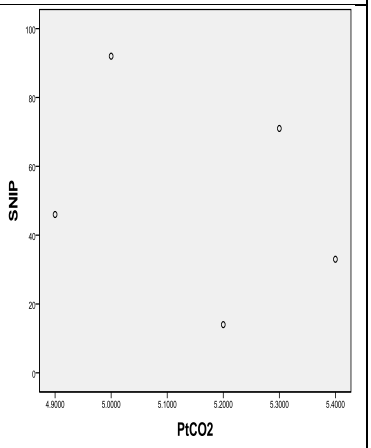
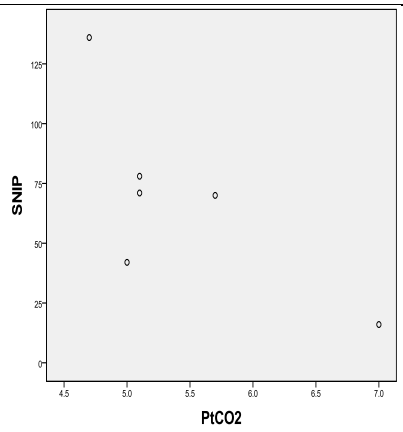
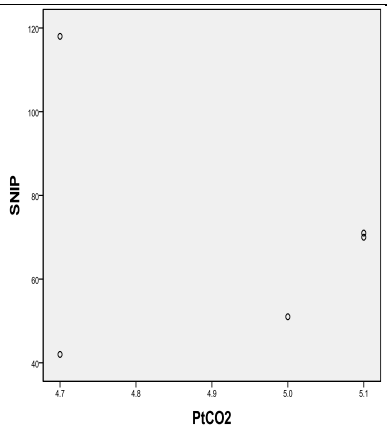
		
Baseline (Pearson Correl. -0.153)	3 months (Pearson Correl. -0.379)	6 months (Pearson Correl. -0.435)
		
9 months (Pearson Correl. -0.196)	12 months (Pearson Correl. -0.380)	15 months (Pearson Correl. -0.199)
		
18 months (Pearson Correl. -0.773)	21 months (Pearson Correl. -0.333)	

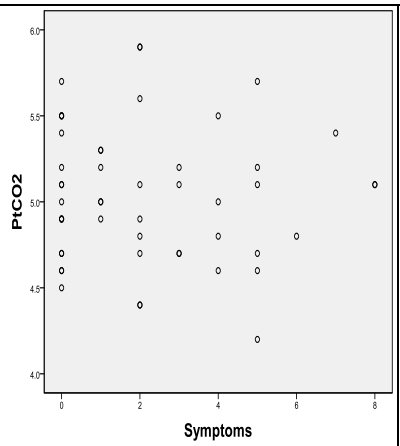
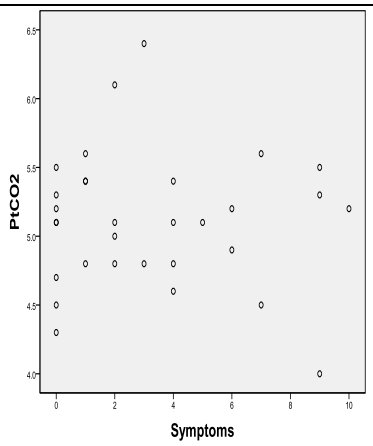
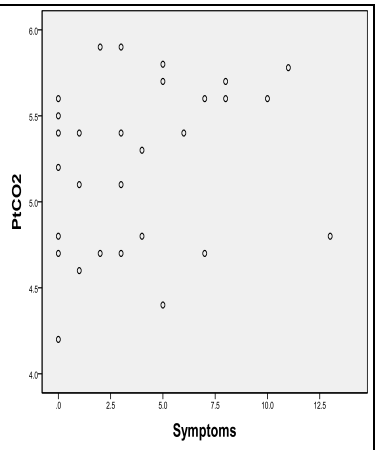
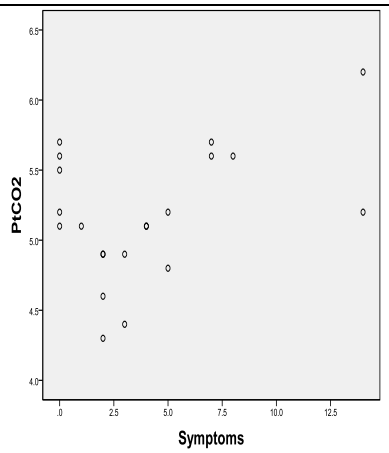
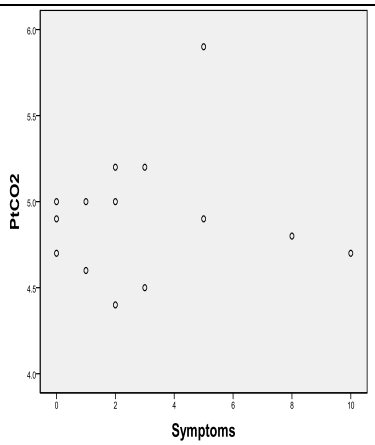
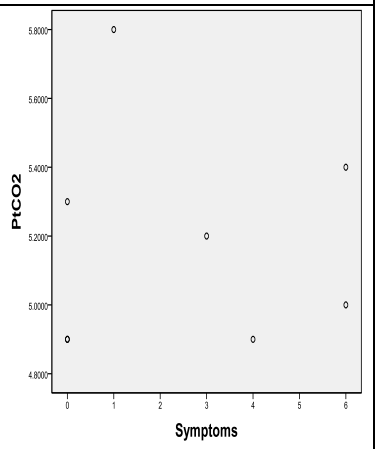
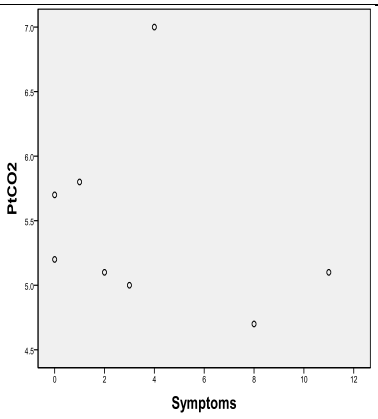
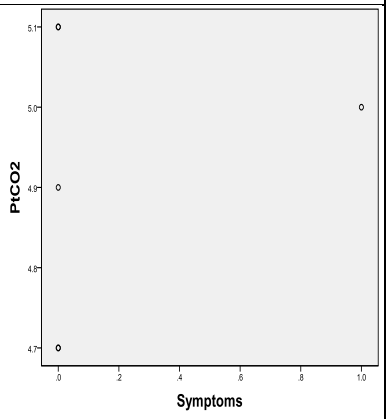
Table 42: Relationship between SNIP and $PtcCO_2$

		
Baseline (Pearson Correl. 0.021)	3 months (Pearson Correl. 0.038)	6 months (Pearson Correl. -0.423)
		
9 months (Pearson Correl. -0.399)	12 months (Pearson Correl. -0.546)	15 months (Pearson Correl. -0.323)
		
18 months (Pearson Correl. -0.738)	21 months (Pearson Correl. -0.238)	

5.9.6) Relationship between symptoms and daytime carbon dioxide level

Table 43 illustrate the relationship between the symptoms of respiratory failure and daytime $PtcCO_2$. No relationship between the symptoms of respiratory failure and daytime $PtcCO_2$ is demonstrated at any of the follow-up time points. Power beyond 12 months, however, is weak due to death of participants and the fact that some participants had not reached that stage of follow-up at the time of writing.

Table 43: Relationship between symptoms and $PtcCO_2$

		
Baseline (Pearson Correl. -0.051)	3 months (Pearson Correl. -0.052)	6 months (Pearson Correl. 0.37)
		
9 months (Pearson Correl. 0.391)	12 months (Pearson Correl. 0.061)	15 months (Pearson Correl. -0.017)
		
18 months (Pearson Correl. -0.267)	21 months (Pearson Correl. 0.22)	

5.9.7) Relationship between day time and nocturnal carbon dioxide levels

Nocturnal transcutaneous capnometry was carried out when respiratory failure was clinically suspected. The difference between day time $PtcCO_2$ and median overnight $PtcCO_2$ was statistically significant (p=0.0002). Table 44 illustrates the difference between the two readings. Figure 24 illustrates the Bland-Altman plot used for the analysis of agreement between the two methods. Pearson correlation coefficient was 0.656.

Table 44: Difference between day time and nocturnal $PtcCO_2$

No.	$PtcCO_2$	$nPtCO_2$	Difference	No.	$PtcCO_2$	$nPtCO_2$	Difference
1	4.9	6.8	1.9	15	6.2	8.0	1.8
2	5.1	6.9	1.8	16	5.9	7.3	1.4
3	Nd	Nd	Nd	17	5.7	7.2	1.5
4	5.5	5.8	0.3	18	5.3	Nd	Nd
5	5.7	5.7	0.0	19	5.3	6.3	1.0
6	5.2	5.5	0.1	20	5.6	6.4	0.8
7	6.1	Nd	Nd	21	5.4	Nd	Nd
8	4.9	9.2	4.3	22	5.2	Nd	Nd
9	5.6	7.2	1.6	23	5.1	Nd	Nd
10	5.4	5.7	0.3	24	5.1	Nd	Nd
11	5.4	6.3	0.9	25	5.3	5.7	0.4
12	7.0	7.2	0.2	26	6.4	Nd	Nd
13	5.8	Nd	Nd	27	5.6	6.8	1.2
14	5.9	Nd	Nd				Nd

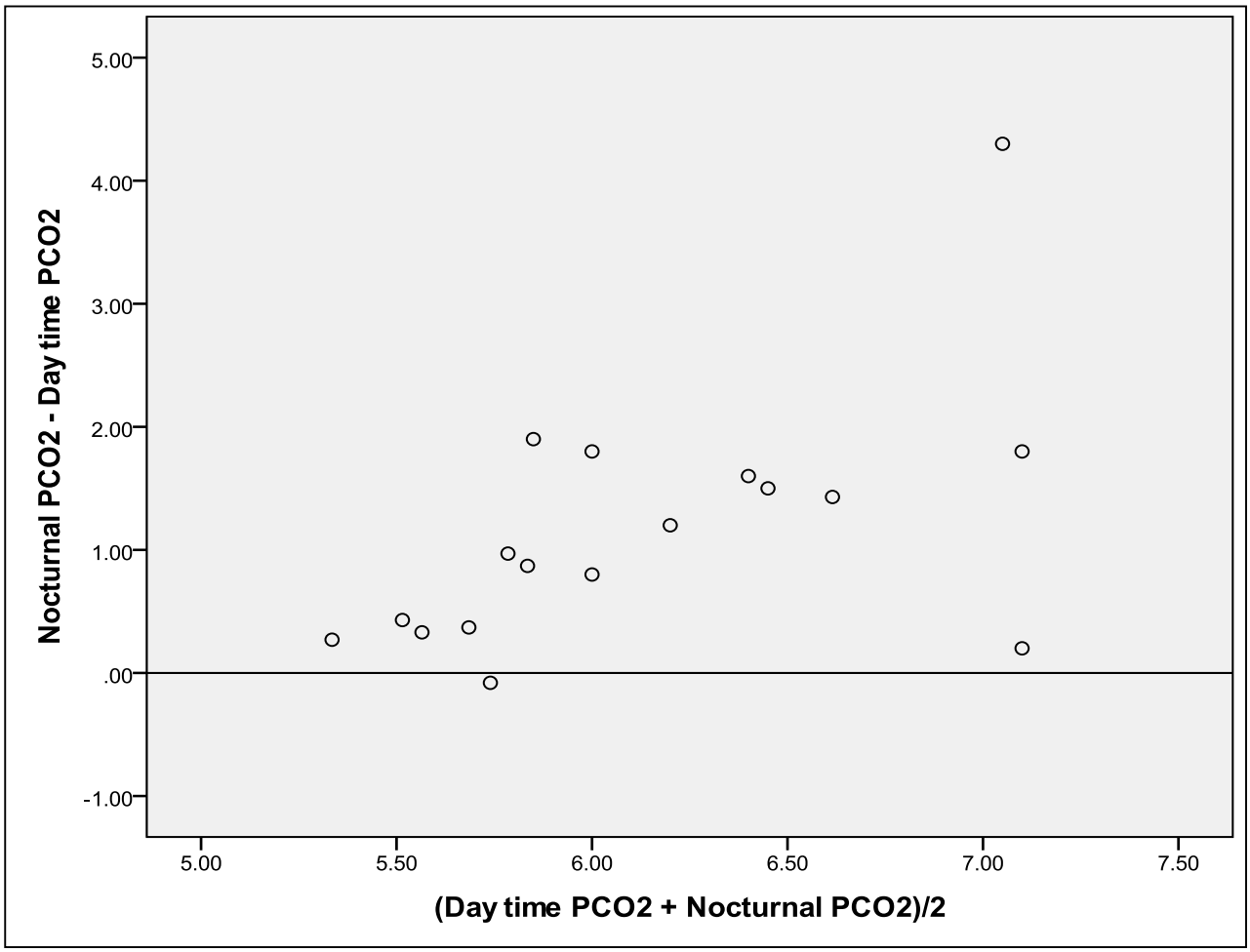


Figure 24: Bland-Altman plot of the difference between the nocturnal and day time PCO_2 against the average of the two measurements

5.10) Discussion

A crucial aspect in the management of patients with motor neurone disease is early identification of respiratory compromise. Respiratory muscle weakness is often unmasked during sleep, particularly during rapid eye movement (REM) sleep when the intercostal and accessory muscles of breathing are inactive and the diaphragm carries the work of breathing[219]. A weak diaphragm may fail to allow adequate ventilation and frequent arousals are required as a compensatory mechanism to maintain adequate ventilation, thus reducing total sleep time, REM sleep and the overall quality of sleep. Hence disturbed sleep, due to episodes of hypoventilation, is one of the earliest manifestations of respiratory insufficiency and usually occurs well before daytime hypoventilation and resulting hypercapnia develops[219]. The symptoms of "sleep fragmentation" include nocturia, nightmares, unrefreshing sleep and daytime somnolence. Symptoms of CO_2 retention include morning headaches, poor appetite, fatigue, cognitive dysfunction and, as a result, poor quality of life. With disease progression, patients may develop exertional dyspnoea, orthopnoea, dyspnoea at rest and anxiety associated with the feeling of breathlessness.

In order to objectively assess respiratory function, a variety of invasive and non-invasive, voluntary and involuntary respiratory function tests have been assessed in order to identify patients with respiratory impairment and plan timely intervention. However, no single respiratory test can reliably confirm or exclude the presence of nocturnal hypoventilation. FVC is a widely used respiratory function test. A FVC of 50% predicts day time hypercapnia with a sensitivity of 53% and specificity of 89%[100], demonstrating the limitations of thos test for predicting even late respiratory failure. Moreover, it is a volitional test which is often difficult for the patients with severe bulbar dysfunction to perform. The most appropriate method to screen for respiratory failure in such patients remains unclear. The ideal test would be non-invasive, easy to perform in an out-patient setting and would diagnose early respiratory failure with high sensitivity. This study was planned with the aim to evaluate the value of regular transcutaneous carbon dioxide measurements in the early detection of respiratory failure. It is non-invasive and independent of the subject being tested and findings are easy to interpret (PCO_2 > 6.0 kPa = respiratory failure). Although daytime hypercapnia is reported in the literature as a relatively late event[189,222], the benefit of regular transcutaneous PCO_2 measurements has not been systematically assessed previously.

There are a number of important lessons learnt in this study. The primary outcome was detection of daytime hypercapnia when it would not have been clinically suspected using other parameters. In the current cohort, no patient was identified to be in respiratory failure on the basis of daytime $PtcCO_2$. Most patients (89%) with other features of respiratory failure and nocturnal hypercapnia, had a normal daytime $PtcCO_2$. This finding suggests daytime compensation of ventilation with the voluntary activation of accessory muscles of breathing and enhanced activation of the respiratory center as a result of improved blood biochemistry. The accessory muscle of respiration and central respiratory drive are both suppressed during normal sleep[219]. Hence, daytime normocapnia may not be considered as indicating the absence of respiratory dysfunction. The importance of symptom history is highlighted in this study. In all the patients analysed thus far, development of symptoms of respiratory compromise (appendix 1) alerted the physicians to the presence of respiratory insufficiency and overnight capnometry was carried out. The most common symptoms identified are listed in Table 36. Based on the most common symptoms, the questionnaire used in this study could be modified further to include only the symptoms listed in Table 36. The resultant questionnaire, with a certain cut-off score, is likely to have a strong positive predictive value in diagnosing respiratory failure. However, such questionnaire would require further validation in diagnosing respiratory failure using a bigger sample size[223]. A difficulty in this regard is in deciding which comparator to use as benchmark of respiratory failure. The best definition of early respiratory failure in patients with neuromuscular disease is nocturnal hypercapnia which requires at least a transcutaneous capnography which is time consuming and expensive. Hence, bedside respiratory function tests need to be combined with clinical assessment to select appropriate patients who are most likely to have nocturnal hypercapnia and may benefit from intervention with NIV.

Once again, the limitations of FVC in predicting respiratory failure is demonstrated in this study. Three patients with confirmed nocturnal hypercapnia had an FVC of greater then 70% predicted. One patient with an FVC of 95% predicted had 6 symptoms of respiratory failure with a median nocturnal $PtcCO_2$ of 6.27 kPa. Similarly an FVC as low as 38% predicted was not associated with any symptoms of respiratory failure. As in tables 39-41, no relationship between symptoms, FVC and $PtcCO_2$ has been demonstrated. Pearson correlation coefficient analysis did not reach significance at any time points and hence further regression analysis to

assess the predictive power of each individual test was not performed. These results slightly disagree with the weak relationship between FVC, SNIP and PCO_2 demonstrated by Lyall *et al* [100]. The most likely explaination is small sample size of this cohort. However, it does highlight the fact that the results of these volitional tests should be interpreted with caution and in a wider clinical context.

In conclusion, regular $PtcCO_2$ measurments may not help in early identification of respiratory failure and daytime normocapnia may be falsely reassuring. Special attention should be given to the presence of symptoms of respiratory failure and overnight capnography carried out where clinical suspicion of respiratory failure is high. Demonstration of nocturnal hypoventilation (rising PCO_2 and falling SpO_2) imply ventilatory failure and the patient may benefit from intervention with NIV.

5.11) Limitations

The study is currently incomplete and 13 participants are still in the follow-up phase. 4 patients died unexpectedly and 6 patients were lost to follow-up and hence excluded from the final analysis.

Although we hypothesised that recording transcutaneous PCO_2 would be particularly valuable for patients with poor bulbar function, only 6 patients with severe bulbar dysfunction could be recruited during the recruitment time available. This precluded a sub-group analysis of patients with significant bulbar impairment.

To calculate sensitivity and specificity (from cross-tabulation) for each of the symptoms of respiratory failure and respiratory function tests, a benchmark is required to detect false negatives and false positives. As stated above, overnight transcutaneous capnography can be used as a gold standard to confirm or exclude hypercapnia. Carrying out overnight capnography at each follow-up time point was however, not feasible with the resources available and was beyond the scope of this study.

Further work is required to validate the robustness of the final version of the questionnaire. This would involve a large sample of patients with MND and normal controls. Also, to establish reliability; test-retest (administration to the same participants at two time points) and inter-

rater consistency (administered by two independent researchers at the same time) criteria need to be satisfied.

CHAPTER 6

GENERAL DISCUSSION AND FUTURE WORK

Increasing developments in the respiratory management of motor neurone disease place more emphasis on careful screening of the patients for evidence of respiratory compromise so that timely interventions can be planned. However, little is known about the most appropriate timing for the initiation of NIV for maximum benefit and bed side tests of respiratory function, which may predict hypercapnia with high sensitivity and specificity, are still lacking. The development of NICE guidelines is an important step forward[208].

In chapter 4, the accuracy of non-invasive transcutaneous carbon dioxide measurements has been assessed. This method has additional benefits of being independent of patient factors and measures partial pressure of carbon dioxide which defines respiratory failure. The results were encouraging and justify the replacement of invasive procedures such as arterial blood gas sampling by transcutaneous measurements. It is expected that this work will promote the use of TOSCA*500* and will add to the current methods of screening for respiratory failure. A high transcutaneous PCO_2 may be accepted as evidence of respiratory failure and such patients may be offered ventilatory support, thus avoiding invasive and time consuming tests. This is especially important in the context of MND, where time spent on investigations is seen by the patients as loss of their quality precious time.

Monitoring day time PCO_2 needs caution. As discussed in chapter 5, a normal daytime PCO_2 may be falsely reassuring as there was a significant difference in the daytime and nocturnal PCO_2 levels. There are important differences in the daytime and nocturnal respiratory physiology. This means that a patient with significant sleep disordered breathing may be able to compensate hypercapnia, resulting from nocturnal hypoventilation, during the day with voluntary effort and increased central respiratory drive. On the other hand, the benefits of correcting early stages of sleep disordered breathing with respiratory support has not be systematically assessed and it has been argued that intervening too early may put the patients off this useful intervention in the more advanced stages of disease. Nevertheless, day time hypercapnia is a late finding and as demonstrated in the study described in chapter 5 is likely to be associated with severe symptoms of respiratory failure. The same study has emphasised the importance of symptom history. All the patients who were suspected to be in respiratory failure on the basis of symptoms (assessed with a structured questionnaire) were confirmed to have significant nocturnal hypoventilation on overnight capnometry. This highlights the need for a well validated, precise questionnaire which is short and easy to administer. The

initial questionnaire (appendix 1) used in the study was purposefully designed to include many questions. It was time consuming to administer but helped in identifying the most common symptoms of respiratory compromise. Appendix 2 is the modified and more concise version which needs validation, but is expected to be of high predictive power, yet quick to administer. Using this questionnaire along with transcutaneous carbon dioxide monitoring would be particularly useful for respiratory assessment in patients with severe bulbar dysfunction who may not be able to perform manoeuvres required for the volitional respiratory function tests. Development of this questionnaire is an important output of this PhD work.

Bedside tests of respiratory function have their own limitations in terms of sensitivity. However, when used with other clinical tools, especially symptom history, they may add value in the overall assessment of patients for evidence of respiratory failure. In chapter 5, poor co-relation of SVC and SNIP with PCO_2 and symptoms of respiratory failure is once again demonstrated. In order to address this gap in technology, non-volitional tests for the assessment of respiratory muscle strength are being developed for clinical use. In this regard phrenic nerve conduction studies to quantify diaphragmatic innervation offers a non-invasive, non-volitional bed-side test of respiratory function[224]. Large studies correlating Phrenic nerve compound motor action potential with symptoms of respiratory insufficiency, FVC, MIP and SNIP and overnight oximetry are desirable to explore this potentially useful clinical tool.

Once respiratory failure has been identified, patients with MND can be offered non-invasive respiratory support. The benefits of NIV on quality of life and survival in MND have been established in a randomised controlled trial and NIV has now become a standard practice in many countries. However, the most optimal timing for initiation of NIV to attain its maximum benefit is unclear. A randomised trial of relatively early initiation of NIV versus standard (as per current practice) would be helpful to answer this question. Evidence suggests that with careful explanation, MND patients can be encouraged to use this intervention at an early stage where symptoms may not be obvious and hence immediate benefits may not be perceived by the recipients[225].

Another important issue surrounding respiratory support is poor tolerance of NIV in patients with severe bulbar dysfunction. The trial by Bourke *et al.* demonstrated a trend of worsening

survival in patients with severe bulbar dysfunction treated with NIV. Clearly there is a need for improving non-invasive respiratory support for patients with severe bulbar dysfunction. The first step towards achieving this goal would be to understand as to why NIV is poorly tolerated in patients with severe bulbar dysfunction. The most likely explanation is difficulty in synchronising their respiratory rhythm with that of the ventilator[226]. Again, evidence suggests that with proper attention to secretion management and prescribed NIV settings, patients with severe bulbar dysfunction may be able to tolerate NIV[227]. Optimal pressure settings of NIV is also an evidence free zone and important clinical lessons can be learnt from a prospective trial of different NIV pressure settings and most comfortable pressure settings for patients with severe bulbar dysfunction can be ascertained. Another potentially useful respiratory support intervention for patients with severe bulbar dysfunction is diaphragmatic pacing. The role of this intervention will become clearer with the publication of the results of the ongoing randomised clinical trial of diaphragm pacing in ALS (DiPALS)[228].

The life expectancy of patients with MND is increasing which leads to many other downstream problems to address. In this regard, inability to cough effectively and remove respiratory secretions is an important issue and considerably adds to the morbidity of MND. Respiratory tract infections precipitating acute-on-chronic respiratory failure is the commonest cause of death in MND. Preventing chest infections with effective cough augmentation could prolong survival. This possibility is highlighted by several retrospective and uncontrolled studies, but the magnitude of benefit has not been assessed in a prospective controlled study. There is also limited knowledge as to how the neural components comprising the cough reflex pathway are affected in MND. Degeneration of the motor component of the vagus nerve contributes to bulbar palsy but it is unknown if degeneration of vagal afferents lining the airways contribute to impaired coughing in MND. Further understanding in this area will be helpful to identify therapeutic targets (e.g., vagus nerve stimulator) to enhance cough reflex in MND.

Chapter 3 describes the first randomised study evaluating the effect of two cough augmentation techniques on pulmonary morbidity, quality of life and survival in MND. The study has demonstrated that survival can be enhanced with cough augmentation without detriment to quality of life, which was also enhanced. Both techniques were well tolerated by patients with good to moderately impaired bulbar function and no significant adverse events

were identified. Of the two techniques, breath-stacking technique was associated with greater survival benefit. However, the difference did not reach statistical significance as the study was not powered for survival analysis. Similarly, the power calculation for pulmonary morbidity was compromised due to lack of data in the literature on pulmonary morbidity following the initiation of NIV for respiratory failure in MND. A larger study is required to explore further the benefits of cough augmentation identified in the present study. The data generated and the lessons learnt in this study will be invaluable for the power calculation and planning of a larger study, with incorporation of more appropriate inclusion criteria. For a larger study, pulmonary morbidity may not be an achievable primary outcome measure. From the results of this study, the probabilities of hospitalisation and chest infection in MND patients using NIV are 25% and 33% per annum respectively. Using these endpoints would lead to an unfeasible sample size calculation: even if the probability were halved (i.e. a relative risk of 0.5), the total sample size would exceed 200. By contrast, differences in overall survival and QoL may be achievable. One option would be to base the sample size on non-inferiority of breath stacking to MI-E, or alternatively to require MI-E to demonstrate a large effect size before it could be considered superior to the breath-stacking technique. This assumption is justified on health economics grounds, as MI-E would not be cost-effective unless it conveyed an advantage of large magnitude. For QoL, if a difference of 0.5SDs in QoL was used as the clinically relevant difference, the resultant trial would need a sample size of 63 per group for 80% power; whilst for overall survival requires a sample size of 54 participants per group with 85% power. It will also be interesting to perform a qualitative study to methodically assess the patients' experience of using their respective cough augmentation techniques.

An important confounder highlighted in this study was compliance with NIV. In this study, patients who tolerated a trial of NIV were considered suitable for recruitment. In retrospect, however, it would have been better to assess patients few weeks following initiation of NIV with recruitment to the cough augmentation study only of those patients who could tolerate NIV for at least for 4 hours overnight for at least 5 days per week. Patients who are non-compliant with NIV are unlikely to gain an important survival benefit with cough augmentation.

Based on the experience obtained in this trial and until a larger scale trial can be conducted, the breath-stacking technique may be used as first line therapy in patients with MND in

respiratory failure. It has also been previously suggested in a physiological study that the breath-stacking technique may be used as a first line intervention and MI-E may be introduced when the breath-stacking technique is no longer effective[157]. There is also a clear health economic benefit of using this inexpensive technique as a first line approach for cough augmentation. MI-E may be offered to individual patients, such as those with profound respiratory muscle weakness with severely limited voluntary insufflation and where the breath-stacking technique becomes ineffective with disease progression. Also, MI-E may have a role in the management of an acute chest infection and in a hospital setting. These potential benefits of MI-E have been highlighted by individual subjects in this study, but need to be explored further in a larger-scale multi-centre study.

As for NIV, the optimal timing for initiating cough augmentation techniques is uncertain. Along with cough augmentation, these techniques also offer a form of chest physiotherapy. Periodic chest expansion, as in natural sighs, are required to maintain pulmonary health. This may be impaired in MND much before respiratory failure is established. Hence, one may argue that maximal chest expansion with cough augmentation techniques should be offered before NIV needs to be initiated. This strategy may have a preventive role, as preventing the first episode of chest infection may be crucial. Once a chest infection has developed, the pulmonary tree may get colonised with bacteria and hence predisposition to recurrent chest infections may not be reversed. Future studies assessing the role of cough augmentation should study the benefits of early intervention.

To achieve sufficient power in respiratory interventional studies in MND is a limiting factor. Adequately powered studies would require multi-centre participation and high cost. Selecting relevant and clinically meaningful primary outcome measures such as QoL (or symptomatic benefit) versus survival also requires careful consideration. Patient and public involvement in research is important in such studies to select the primary outcome measure most important to the patients with MND and their carers. In a rapidly progressive and disabling disease like MND comfort and QoL may be more relevant when considering an intervention. Future studies should be planned with due consideration of these issues and symptomatic therapies for MND should continue to develop while awaiting a cure for this devastating disease.

In conclusion, the body of work described in this is PhD has contributed to the current knowledge regarding respiratory assessment and management in MND. Also, it has identified areas for further development and research.

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APPENDICES

Appendix 1

Screening questionnaire to identify MND patients with respiratory failure

Do you suffer from any of the following? Please tick yes or no column

Breathing related symptoms	**Yes**	**No**
Have you noticed any change in your breathing? If yes please specify ……. ……		
Is there anything which makes you short of breath (e.g. on walking, eating, bathing, dressing etc?) If yes, please mention the least strenuous activity ……..		
Do you get short of breath when lying flat?		
Do you have difficulty coughing?		
Sleep related symptoms		
Have you noticed any change in your sleeping pattern? If yes, please specify ……		
Do you ever wake up feeling short of breath?		
Is your sleep disturbed/interrupted? If yes, please specify why …… How many times do you wake up …….. How long do you sleep in between …….		
Do you get up at night to pass urine more than usual?		
Do you feel refreshed on awakening?		
Do you have early morning headaches?		
Do you feel sleepy during the day (more than usual)?		
Do you fall asleep inappropriately?		
Do you feel drowsy or fight to stay alert during the day?		
Mental/emotional state		
Have you noticed any change in your usual self (e.g. irritable, anxious, low mood etc) If yes, please specify ……		
Do you feel fatigued or lack of energy?		
Do you have poor motivation to do things which you can do?		
Have you lost your appetite?		
Do you find hard to concentrate?		

Appendix 2

Screening questionnaire to identify MND patients with respiratory failure

Do you suffer from any of the following? Please tick yes or no column

Breathing related symptoms	**Yes**	**No**
Have you noticed any change in your breathing? If yes please specify ……		
Is there anything which makes you short of breath (e.g. on walking, eating, bathing, dressing etc?) If yes, please mention the least strenuous activity ……..		
Do you have difficulty coughing?		
Sleep related symptoms		
Is your sleep disturbed/interrupted? If yes, please specify why …… How many times do you wake up …….. How long do you sleep in between …….		
Do you feel sleepy during the day (more than usual)?		
Mental/emotional state		
Do you feel fatigued or lack of energy?		
Have you lost your appetite?		

Appendix 3 (Participant diary)

Evaluation of the impact of breath-stacking on morbidity, quality of life and survival in patients with motor neurone disease (MND) using non-invasive ventilation (NIV)

Participant Diary

Details about you

Name

Address

Date of Birth

Telephone No

Date started on NIV

Date started on Breath-stacking

How to use this diary:

- This diary tells you about…
  - Infections and how to avoid them
  - Things you need to tell your doctors
  - Medicines you take at home

- Your doctors will use this diary to…
  - Record details of your treatment
  - Tell you who to contact in an emergency

- To help your doctors, please
  - Make a note of any side effects you have during treatment
  - Write down any medicines to take regularly

- You may also like to…
  - Record your medical appointments
  - Make you own notes

What is Breath-stacking?

Breath-stacking is breathing technique that is designed to help patients develop greater lung capacity, and to improve power of cough.

Breath-stacking involves taking 3 to five breathes in to fill the lung space, before breathing out slowly. It is performed using a mask or mouth piece and an ambubag.

Benefits of Breath-stacking

- Increases lung capacity
- Can help to improve power of cough
- Safe and non-invasive
- Easy for patients and caregivers to operate

Breath-stacking Flexibility

- Can be used with a face mask, mouthpiece or with an adapter to a patient's endotracheal or tracheostomy tube

Respiratory Tract Infections

Watch out for the signs of infection listed here. If you spot any of them contact your GP straight away, as you may need treatment with antibiotics.

- Persistent cough
- Cough-up mucous
- Breathlessness
- Wheezing
- Dry mouth
- High temperature
- Uncontrollable shivering / shaking
- Headache

Please tell your doctors if you have any symptoms – the sooner we know the sooner we can treat them

How to fill in your diary

Symptoms:

The most common symptoms of a chest infection are listed down the left hand side of the diary page. Place a tick in the box for each day you experience the symptom.

If you experience any other symptoms, please tick the other box and make a note of them on the notes page at the end of each month

Contacts:

Place a tick in the box for each time you contact any of the people listed in the left hand column.

If you contact anyone else about your illness of treatment, please tick the other box and make a note of this on the notes page at the end of each month

Other:

Please put a tick in the box for each of the days you take antibiotics or are in hospital

Please write down the number of times you use breath-stacking technique

If anything else occurs please put a tick in the other box and make a note of on the notes page at the end of the month

There also a space in which we would like you to record the medication that you are taking. You can ask your doctor to fill this in for you if you are not sure about anything

We have put down examples of what your diary might look like for you to look at on the next three pages

Let us answer your questions

If you have any questions then please get in touch with us using the contacts on the last page of this diary. There is also some space for you to write down any thoughts or questions you may want to ask your consultant when you next see them

Remember we are here to take care of you and give you information about your treatment, **so please ask**

JANUARY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Symptoms:																
Persistent cough				√	√	√	√	√	√	√						
Coughing-up mucous						√	√	√	√							
Breathlessness	√	√	√	√	√	√	√	√	√							
Wheezing			√	√	√	√	√	√	√	√						
Dry mouth		√	√	√	√	√	√	√	√	√	√					
High temperature					√	√	√	√								
Headache							√									
Shivering / shaking																
Other:																
Contacted:																
GP					√											
District Nurse																
Research Nurse																

Research Doctor																
Consultant																
Helpline					√											
Other:								√								
Other:																
Prescribed Antibiotics					√	√	√	√	√	√	√	√				
Number of times used Breath-stacking	2	2	2	2	3	3	4	5	3	2	2	2	2	2	2	2
Admitted to hospital																
Other:																

JANUARY	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Symptoms:																
Persistent cough																
Coughing-up mucous																
Breathlessness																
Wheezing																
Dry mouth																
High temperature																
Headache																
Shivering / shaking																
Other:																
Contacted:																
GP																
District Nurse																

Research Nurse							√									
Research Doctor							√									
Consultant							√									
Helpline																
Other:																
Other:																
Prescribed Antibiotics																
Number of times used Breath-stacking	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
Admitted to hospital																
Other:																

Notes:

5th January: Rang helpline about being able to use machine more than two times in one day

8th January: Seen by physio for help with breathing - coughing up phlegm

23rd January: Appointment with consultant at hospital. Saw research doctor and the nurse too

Current medication:

Symptoms:																
Persistent cough																
Coughing-up mucous																
Breathlessness																
Wheezing																
Dry mouth																
High temperature																
Headache																
Shivering / shaking																
Other:																
Contacted:																
GP																
District Nurse																
Research Nurse																

Research Doctor																
Consultant																
Helpline																
Other:																
Other:																
Prescribed Antibiotics																
Number of times used Breath-stacking																
Admitted to hospital																
Other:																

PUBLICATIONS RESULTING

FROM THIS PHD

Part of this thesis has been published as part of the following communications. I have retained the right to publish the material in this thesis and consent from co-authors has been obtained.

Peer-reviewed journal research articles

1. Rafiq MK, Bradburn M, Proctor AR, Billings C, Bianchi S, McDermott CJ, Shaw PJ. Effects of cough augmentation on pulmonary morbidity, survival, and quality of life in patients with amyotrophic lateral sclerosis in respiratory failure: a randomised trial. 2014 (Submitted)
2. Rafiq MK, Bradburn M, Proctor AR, Billings C, Bianchi S, McDermott CJ, Shaw PJ. Using transcutaneous carbon dioxide monitor (TOSCA 500) to detect respiratory failure in patients with Amyotrophic Lateral Sclerosis: a validation study. Amyotrophic Lateral Sclerosis. October 2012, Vol. 13, No. 6, Pages 528-532.
3. Rafiq MK. Response to letter to the editor. Amyotroph Lateral Scler Frontotemporal Degener. 2013 Sep;14(5-6):481.

Peer-reviewed systematic review

4. Radunovic A, Annane D, Rafiq MK, Mustfa N. Mechanical Ventilation in Amyotrophic Lateral Sclerosis (up dated Cochrane Review). Cochrane Database of Systematic Reviews. 2013.

Peer-reviewed journal review articles

5. Rafiq MK. Motor neuron disease. Geriatric Medicine mid-life and beyond. 2012 Oct.
6. Rafiq MK, Proctor AR, McDermott CJ, Shaw PJ. Respiratory management of motor neurone disease: a review of current practice and recent developments. Practical Neurology. 2012 (12):166-176.

Peer-reviewed journal editorial

7. Rafiq MK. Non-invasive ventilation (NIV) in patients with amyotrophic lateral sclerosis (ALS).Physiotherapy. 2013 Mar;99(1):92. doi: 10.1016/j.physio.2012.07.002. Epub 2012 Jul 21.

Conference abstracts and presentations

1. **American Academy of Neurology annual meeting Philadephia 2014**

   Rafiq MK, Bradburn M, Proctor AR, Billings C, Bianchi S, McDermott C, Shaw PJ. Effects of cough augmentation on pulmonary morbidity, survival and quality of life in patients with Amyotrophic lateral sclerosis in respiratory failure: a randomised controlled trial.

2. **International Symposium on ALS/MND Milan 2013**

   Rafiq MK, Bradburn M, Proctor AR, Billings C, Bianchi S, McDermott C, Shaw PJ. Effects of cough augmentation on pulmonary morbidity, survival and quality of life in patients with Amyotrophic lateral sclerosis in respiratory failure: a randomised controlled trial. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. November 2013, Vol. 14, No. S2, Pages 84-94.

3. **North of England Neurological Association Annual Meeting Harrogate 2013**

   Rafiq MK, Bradburn M, Proctor AR, Billings C, Bianchi S, McDermott C, Shaw PJ. Effects of cough augmentation on pulmonary morbidity, survival and quality of life in patients with Amyotrophic lateral sclerosis in respiratory failure: a randomised controlled trial. Awarded the Crawford Prize for clinical research.

4. **International Symposium on ALS/MND Chicago 2012**

   MK Rafiq, PJ Shaw. Clinical evaluation of transcutaneous carbon dioxide monitor (TOSCA) in patients with Motor Neurone Disease

5. **Association of British Neurologists Annual Meeting Brighton 2012**

   MK Rafiq, AR Proctor, CJ McDermott, PJ Shaw. Clinical evaluation of transcutaneous carbon dioxide monitor (TOSCA) in patients with Motor Neurone Disease. *J Neurol Neurosurg Psychiatry 2012;83:Suppl 2 A32-A33 doi:10.1136/jnnp-2012.*

6. **North of England Neurological Association Annual Meeting Harrogate 2011**

   MK Rafiq. Clinical evaluation of transcutaneous carbon dioxide monitor (TOSCA) in patients with Motor Neurone Disease.